INCREASING IMPORTANCE OF PATIENTS-GENERATED REAL WORLD DATA FOR HEALTHCARE POLICY DECISIONS ABOUT MEDICINAL PRODUCTS

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Impact of Cost-Related Medication Nonadherence on Economic Burdens, Productivity Loss, and Functional Abilities: Management of Cancer Survivors in Medicare

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Background: Cancer survivors are vulnerable to have medication nonadherence. We aimed to estimate the impact of cost-related medication nonadherence on economic burdens, productivity loss, and functional abilities among cancer survivors.

Methods: A cross-sectional study was conducted using data from the National Health Interview Survey (NHIS), 2011–2018. Cost-related medication nonadherence was identified based on NHIS prompts. An ordinal logistic regression model was used to determine the impact of cost-related medication nonadherence on survivors' economic burden. Two negative binomial regression models were implemented to estimate the impact on productivity loss. In addition, four logistic regression models were used to determine the impact on functional abilities. The weighted analysis was used to generate national estimates.

Results: Among 35, 773, 286 cancer survivors, 15, 002, 192 (41.9%) respondents reported that they experienced cost-related medication nonadherence. Compared to cancer survivors without cost-related medication nonadherence, those with nonadherence were significantly associated with an increased economic burden (OR: 1.89, 95% CI: 1.70–2.11). Also, cancer survivors with cost-related medication nonadherence were significantly more likely to have an increased bed disability day (IRR: 1.46, 95% CI: 1.21–1.76). In terms of the limitations, cancer survivors with nonadherence were significantly more likely to have both activity limitation (OR: 1.42, 95% CI: 1.25–1.60) and functional limitation (OR: 2.12, 95% CI: 1.81–2.49).

Conclusion: Cost-related medication nonadherence increased economic burdens, productivity loss, and limitations in functional abilities among cancer survivors. Strategies are needed to help cancer survivors with cost-related medication nonadherence to be adherent to prescriptions.

Keywords: cost-related medication nonadherence, economic burdens, productivity loss, functional abilities, cancer survivors

BACKGROUND

An estimated 16.9 million cancer survivors were living in the United States in 2019 (American Cancer Society, 2019). Due to the potential increase in the size of the population, the number of cancer survivors is estimated to increase to 22.1 million in 2030 (American Cancer Society, 2019). Cancer survivors are often treated with extensive and expensive treatments such as chemotherapy, immunotherapy, and nonpharmacological treatments (Baskar et al., 2012). Since cancer survivors are more likely to have chronic comorbidities, they have to be treated for those chronic illnesses as well (Mirza et al., 2018). Due to the high costs of the medications in the treatment and the treatment itself, cancer survivors are more than twice as likely to not adhere to medication treatments (Zhang and Meltzer, 2015; Smith et al., 2019; Zhao et al., 2019).

With the development of innovative interventions for cancer, the death rate of cancer has been decreasing continuously (Siegel et al., 2019), but cancer survivors consequently face a heavier economic burden due to the treatment in their extended life years (Carlotto et al., 2013). Evidence shows that the medical costs for cancer care had increased annually regardless of the type of cancer from 2010 to 2017 in the United States and the total medical costs of cancer care are projected to increase to $157.8 billion by 2020 (Mariotto et al., 2011; Guy et al., 2017). For cancer survivors, although medication nonadherence might decrease pharmacy costs, it could significantly increase other costs, such as hospital costs and indirect costs (Cutler et al., 2018). Cost-related medication nonadherence to cancer medications has been shown to increase the total healthcare costs (Nekhlyudov et al., 2011; Kaul et al., 2017). Given an increased likelihood of comorbidities caused by medication nonadherence, costs for other chronic conditions may increase (Cutler et al., 2018). Cancer survivors with cost-related medication nonadherence are more likely to have a worse quality of life due to the disease progression led by insufficient but necessary health care (Meneses et al., 2012; Fenn et al., 2014). Under the situation of insufficient health care and lower quality of life, cancer survivors may lose more productivity and have a worse condition of functional abilities (Bouwman et al., 2017; Martin et al., 2018; Chou et al., 2019).

However, little is known about the association between cost-related medication nonadherence and economic burdens among cancer survivors. No literature has shown the potential impact of cost-related medication nonadherence on cancer survivors' productivity loss and functional abilities. This study used a retrospective pooled cross-sectional study with the National Health Interview Survey (NHIS), a large nationally representative cohort study of United States adults, to study the impact of cost-related medication nonadherence on economic burdens, productivity loss, and functional abilities among cancer survivors.

METHODS

Data and Study Population

This is a retrospective pooled cross-sectional study using the data from the NHIS, 2011–2018. The NHIS is an ongoing, national, long-term, cross-regional, annual family interview survey of the civilian non-institutionalized United States population, held annually by the National Center for Health Statistics (NCHS) of the Centers for disease Control and Prevention (CDC) (National Center for Healt, 2020). NHIS sample is designed and weighted to be representative of the United States population, using a multistage probability sample design (National Center for Healt, 2020). The detailed sampling and survey methods of NHIS are provided elsewhere (Parsons et al., 2014). We used NHIS because it collected information on cancer survivors annually.

The period of 2011–2018 was used because the information on cost-related medication nonadherence started being reported in 2011 and 2018 is the latest data available. We included cancer survivors aged 18 years or older. To be consistent with previous studies on cancer survivors using NHIS, we excluded cancer survivors with only nonmelanoma skin cancers (Greenlee et al., 2016; Boyd et al., 2020; Dee et al., 2020). Also, we excluded cancer survivors who had an unknown or missing value on NHIS prompts of cost-related medication nonadherence.

Measures

Cancer survivors were identified if they have ever been told by a doctor or other health professional that they had cancer. Cost-related medication nonadherence was defined as the failure to make the required prescriptions due to costs, and cancer survivors with cost-related medication adherence were determined if they had answered "yes" to any of the following prompts: "During the past 12 months, in order to save money, did you 1) delay refilling prescription? 2) Take less medication? 3) Skipped medication doses?" The economic burden was measured as the amount of family health care spending in the past 12 months, which was categorized into four levels ($0, $1-$1,999, $2,000–4,999, $5,000 or more). Productivity loss was measured as the work-loss days and bed disability days of the survivors in the past 12 months. Limitations included activity limitation, functional limitation, activities of daily living (ADL) limitation, and instrumental activities of daily living (IADL) limitation. Specifically, ADL refers to an individual's daily self-care activities, while IADL indicates daily activities that require more complex interactions (Katz, 1983). Activity and functional limitations were determined if respondents answered "yes" to the relevant prompts asking whether they had the limitation in the past 12 months. ADL limitation was identified if respondents answered "yes" to an NHIS prompt asking whether they needed help with daily self-care activities, such as eating, bathing, dressing, or getting around inside the house. IADL limitation was identified if respondents answered "yes" to an NHIS prompt asking whether they needed help in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes.

Five demographic variables were included as covariates: age (18–29, 30–44, 45–64, and ≥65), gender (male and female), race (non-Hispanic White, non-Hispanic Black, Hispanic, and others), marital status (single and non-single), and census region (Northeast, North, Central/Midwest, South, and West); three socioeconomic variables were included as covariates:

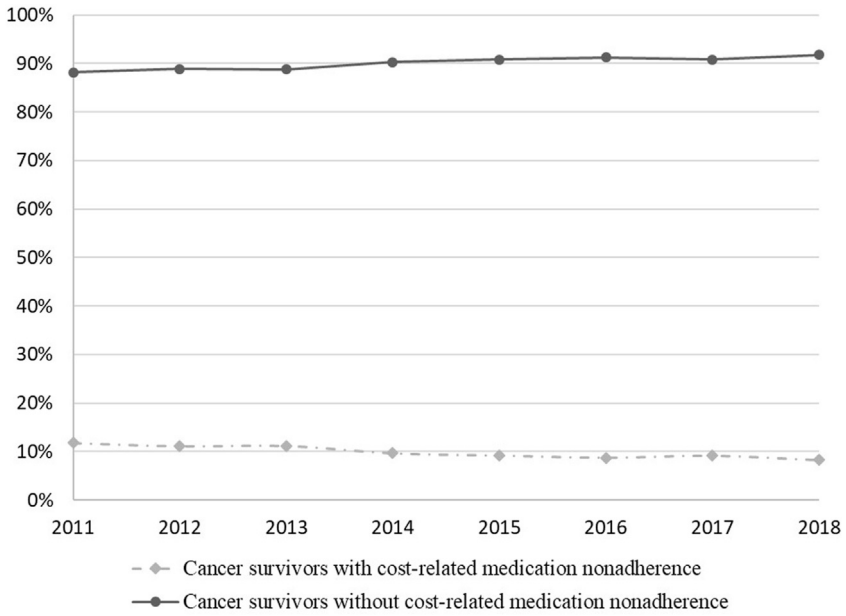

FIGURE 1 | Trend of cost-related medication nonadherence among cancer survivors between 2011 and 2018.

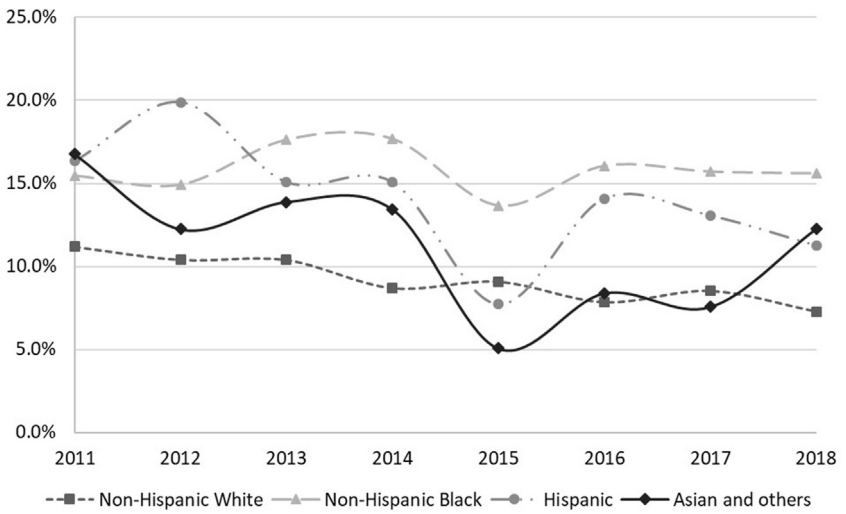

FIGURE 2 | Racial/ethnic disparities in cost-related medication nonadherence among cancer survivors between 2011 and 2018.

education attainment (below high school, high school, above high school), family income (<$50,000, $50,000–$99,999, ≥$100,000), and health care insurance (yes and no); and two physical health-related variables: body mass index (BMI) (<18.5, 18.5–24.9, 25–29.9, and ≥30) and general health status (good/very good/excellent, fair/poor).

Statistical Analysis

The chi-square and *t*-test were used to compare the baseline characteristics between cancer survivors who reported cost-related medication nonadherence and those who did not. The prevalence of cost-related medication adherence was measured using the number of respondents who reported cost-related medication nonadherence divided by the total number of respondents. Logistic regression models were used to identify if there was a significant trend of the cost-related medication nonadherence by using the prevalence as the dependent variable and the year as the independent variable. We performed an ordinal logistic regression model to examine the impact of cost-related medication nonadherence on economic burdens,

TABLE 1 | Baseline characteristics of cancer survivors with or without cost-related medication nonadherence.

Characteristics	With cost-related medication nonadherence (*n* = 2,302)	Without cost-related medication nonadherence (*n* = 20,606)	*P*-Value
	Sample No. (weighted %), Mean (SE)	Sample No. (weighted %), Mean (SE)	
Year			<0.001
2011	348 (12.4%)	2494 (15.2%)	
2012	369 (12.4%)	2679 (14.2%)	
2013	306 (11.2%)	2370 (12.9%)	
2014	292 (11.3%)	2684 (11.1%)	
2015	258 (12.1%)	2617 (11.2%)	
2016	272 (13.1%)	2953 (11.5%)	
2017	244 (13.2%)	2431 (12.2%)	
2018	213 (14.2%)	2378 (11.7%)	
Age			<0.001
≥18 and <30	92 (1.4%)	278 (3.8%)	
≥30 and <45	334 (5.4%)	1110 (14.4%)	
≥45 and <65	1157 (30.1%)	6141 (50.6%)	
≥65	719 (63.1%)	13077 (31.3%)	
Gender			<0.001
Female	650 (29.2%)	8665 (41.9%)	
Male	1652 (70.8%)	11941 (58.1%)	
Marital status			<0.001
Married	814 (36.2%)	9827 (48.3%)	
Non-married	1484 (63.8%)	10742 (51.7%)	
Race/ethnicity			<0.001
Non-hispanic white	1756 (79.6%)	17341 (86.6%)	
Non-hispanic black	287 (10.8%)	1541 (6.3%)	
Hispanic	173 (6.4%)	1036 (4.4%)	
Other[a]	86 (3.1%)	688 (2.8%)	
Living region			<0.001
Northeast	286 (13.3%)	3659 (18.3%)	
North central/Midwest	525 (25.4%)	4831 (24.3%)	
South	942 (41.1%)	7182 (36.5%)	
West	549 (20.2%)	4934 (20.9%)	
Education			<0.001
Below high school	378 (14.7%)	2688 (12.1%)	
High school graduate	597 (26.6%)	5318 (25.4%)	
Above high school	1327 (58.7%)	12600 (62.5%)	
Family income			<0.001
< $50,000	1659 (73.3%)	10147 (51.2%)	
≥ $50,000 and < $100,000	414 (19.6%)	5277 (28.4%)	
≥ $100,000	139 (7.1%)	3574 (20.4%)	
Health status			<0.001
At least good	1092 (24.3%)	5176 (46.5%)	
Poor or fair	1209 (75.7%)	15414 (53.5%)	
BMI			<0.001
<18.5	56 (2.2%)	408 (1.9%)	
≥18.5 and <25	574 (25.7%)	6359 (31.3%)	
≥25 and <30	669 (29.3%)	7245 (35.4%)	
≥30	1003 (42.8%)	6594 (31.5%)	
Health insurance			<0.001
No	927 (39.1%)	6296 (30.4%)	
Yes	1374 (60.9%)	14279 (69.6%)	
Family healthcare spending			<0.001
$0	127 (5.2%)	1664 (8%)	
> $0 and < $2,000	1323 (57.9%)	12891 (63.5%)	
≥ $2,000 and < $5,000	525 (23.9%)	3754 (19%)	
≥ $5,000	297 (13%)	1801 (9.5%)	
Activity limitation			<0.001
No	1004 (44.4%)	12962 (63.5%)	
Yes	1296 (55.6%)	7635 (36.5%)	
Function limitation			<0.001
No	372 (16.3%)	6777 (33.4%)	
Yes	1929 (83.7%)	13813 (66.6%)	

(Continued on following page)

TABLE 1 | (*Continued*) Baseline characteristics of cancer survivors with or without cost-related medication nonadherence.

Characteristics	With cost-related medication nonadherence (*n* = 2,302)	Without cost-related medication nonadherence (*n* = 20,606)	*P*-Value
	Sample No. (weighted %), Mean (SE)	Sample No. (weighted %), Mean (SE)	
ADL limitation			<0.001
No	2108 (92.1%)	19376 (94.1%)	
Yes	194 (7.9%)	1228 (5.9%)	
IADL limitation			<0.001
No	1904 (83.4%)	18114 (88.2%)	
Yes	398 (16.6%)	2487 (11.8%)	
Work-loss days	8.08 (0.37)	13.04 (1.28)	<0.001
Bed disability days	8.35 (0.28)	24.31 (1.52)	<0.001

ADL: activities of daily living; BMI: body mass index; IADL: instrumental activities of daily living; SE: Standard error.
[a]*Other includes Asian, Aleut, Alaskan Native, or American Indian, Pacific Islander, Hawaiian, Samoan, Guamanian, and multiple races.*

two negative binomial regression models for the impact on productivity loss, and four logistic regression models for the impact on limitations. The results of the logistic regression models were reported as odds ratios (OR) with 95% confidence intervals (CI), while the results of the negative binomial regression models were reported as incidence rate ratios (IRR) with 95% confidence intervals (CI).

All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). NHIS-constructed survey weights were applied to account for the NHIS complex stratified sampling methods and to make estimates that are representative of the United States civilian non-institutionalized population.

RESULTS

Among 22,908 cancer survivors, 2,302 (10.0%) respondents reported that they had cost-related medication nonadherence in the past 12 months. After weighting, among 75, 690, 823 cancer survivors, 7,464,168 (9.8%) reported cost-related medication nonadherence. There was a decreasing trend of cost-related medication nonadherence among cancer survivors between 2011 and 2018 ($p < 0.001$, **Figure 1**). The trend by race and ethnicity showed that among cancer survivors, only the trend in non-Hispanic Whites was continuously decreasing, while there was no specific pattern of the trends among other races (**Figure 2**). Compared to non-Hispanic Whites, non-Hispanic Blacks and Hispanics reported a higher prevalence of cost-related medication nonadherence.

Table 1 demonstrated the comparisons of baseline characteristics between cancer survivors with or without cost-related medication nonadherence. All characteristics were significantly different between cancer survivors with or without cost-related medication nonadherence. Compared with cancer survivors without cost-related medication nonadherence, those with nonadherence were more likely to have a higher economic burden ($p < 0.001$), more activity limitation ($p < 0.001$) and more functional limitation ($p < 0.001$), as well as more likely to need the help of ADL ($p < 0.001$) and IADL ($p < 0.001$). In addition, cancer survivors with cost-related medication nonadherence had longer average work-loss days ($p < 0.001$) and bed disability days ($p < 0.001$).

In the multivariable analysis, we found that compared to cancer survivors without cost-related medication nonadherence, those with the nonadherence were associated with a higher economic burden (OR: 1.89, 95% CI: 1.70–2.11) (**Table 2**). Cancer survivors with cost-related medication nonadherence were more likely to have an increased bed disability day (IRR: 1.46, 95% CI: 1.21–1.76) (**Table 2**). However, the association between cost-related medication nonadherence and the increased work-loss day was not significant. In terms of functional abilities, cancer survivors with nonadherence were more likely to have both activity limitation (OR: 1.42, 95% CI: 1.25–1.60) and functional limitation (OR: 2.12, 95% CI: 1.81–2.49) (**Table 3**). The association of cost-related medication nonadherence with either ADL limitation (OR: 0.90, 95% CI: 0.73–1.11) or IADL limitation (OR: 0.98, 95% CI: 0.83–1.16) was not significant.

DISCUSSION

Using a nationally representative dataset, our study examined the impact of cost-related medication nonadherence on economic burdens and productivity as well as activity limitation and functional limitation among cancer survivors. We found that there was a significant decreasing trend in the self-reported cost-related medication nonadherence throughout the study period. Also, the results showed that cost-related medication nonadherence is significantly associated with increased economic burdens and productivity loss. Cancer survivors were more likely to have worse functional abilities.

The significant decreasing trend of cost-related medication nonadherence to health care might be because of the Patient Protection and Affordable Care Act (ACA), which was implemented in 2011, and the majority of substantial changes were nationally implemented in 2014 that was covered by the period of our study (Dresden et al., 2017). With the enaction of ACA, more affordable health insurance plans were aimed to be established, thereby lowering the total medical costs for low-income households (French et al., 2016; Dresden et al., 2017). In

TABLE 2 | The impact of cost-related medication nonadherence on economic burdens and productivity loss among cancer survivors.

Variables	Economic burdens, OR (95% CI)[a]	Work-loss days, IRR (95%CI)[a]	Bed disability days, IRR (95% CI)[a]
Cost-related medication nonadherence			
No	Ref		
Yes	1.89 (1.70–2.11)	1.28 (0.92–1.78)	1.46 (1.21–1.76)
Age			
≥18 and <30	Ref		
≥30 and <45	1.58 (1.16–2.16)	1.93 (1.28–2.92)	1.38 (0.92–2.07)
≥45 and <65	1.84 (1.36–2.49)	1.33 (0.95–1.87)	1.03 (0.73–1.47)
≥65	1.52 (1.13–2.05)	0.90 (0.59–1.37)	0.66 (0.46–0.95)
Sex			
Female	Ref		
Male	0.99 (0.92–1.05)	1.20 (0.98–1.47)	1.72 (1.43–2.05)
Marital status			
Married	Ref		
Non-married	0.53 (0.50–0.57)	0.91 (0.74–1.11)	0.84 (0.71–1.00)
Race/ethnicity			
Non-hispanic white	Ref		
Non-hispanic black	0.50 (0.44–0.57)	1.54 (0.89–2.64)	1.32 (0.95–1.82)
Hispanic	0.69 (0.58–0.82)	1.14 (0.75–1.74)	1.52 (1.07–2.16)
Other[b]	0.66 (0.53–0.82)	1.37 (0.67–2.80)	1.20 (0.90–1.61)
Living region			
Northeast	Ref		
North central/Midwest	1.17 (1.06–1.29)	0.90 (0.68–1.19)	0.92 (0.65–1.29)
South	1.22 (1.11–1.33)	1.11 (0.84–1.45)	0.95 (0.69–1.30)
West	1.18 (1.07–1.32)	1.24 (0.91–1.68)	0.98 (0.71–1.37)
Education			
Below high school	Ref		
High school graduate	1.29 (1.15–1.44)	1.23 (0.78–1.95)	0.95 (0.69–1.30)
Above high school	1.68 (1.50–1.88)	0.91 (0.59–1.41)	0.90 (0.67–1.22)
Family income			
< $50,000	Ref		
≥ $50,000 and < $100,000	1.93 (1.78–2.09)	0.98 (0.76–1.27)	0.77 (0.63–0.93)
≥ $100,000	2.62 (2.36–2.91)	0.82 (0.61–1.11)	0.80 (0.59–1.08)
Health insurance			
No	Ref		
Yes	1.05 (0.98–1.13)	1.35 (1.00–1.82)	0.95 (0.76–1.19)
BMI			
<18.5	Ref		
≥18.5 and <25	0.97 (0.76–1.25)	1.65 (0.80–3.39)	1.51 (0.94–2.42)
≥25 and <30	0.96 (0.89–1.04)	0.93 (0.72–1.20)	0.89 (0.70–1.11)
≥30	0.98 (0.90–1.06)	1.03 (0.79–1.34)	0.90 (0.74–1.11)
Health status			
At least good	Ref		
Poor or fair	1.15 (1.11–1.19)	1.85 (1.66–2.06)	2.29 (2.13–2.46)

BMI: body mass index; CI: Confidence interval; OR: Odds ratio.

[a]*The results are weighted.*

[b]*Other includes Asian, Aleut, Alaskan Native, or American Indian, Pacific Islander, Hawaiian, Samoan, Guamanian, and multiple races.*

addition, ACA encouraged the expansion of Medicaid program coverage to allow more adults in most states to be financially capable of receiving their treatment with less stress regarding billing issues (Mechanic, 2014). Such measures outlined in ACA might help gradually reduce the prevalence of cost-related medication nonadherence among cancer survivors (Dresden et al., 2017).

Contrary to the purpose of saving money, cost-related medication nonadherence led to an unintended consequence that was associated with an increased amount of family health care costs, which was likely due to a number of varying factors. Evidence has shown that medication nonadherence is associated with an increase in complications of chronic conditions and hospital visits (Kaul et al., 2017). Also, medication nonadherence is associated with the progression of the disease for cancer survivors, which is likely to worsen the quality of life of patients (Shafrin et al., 2017; Zhou et al., 2019). Given an increase in the amount of annual health care utilization and a worse quality of life, it is likely there would be an increase in the costs of patients (Epstein et al., 2017; Sawaya et al., 2019). Similar results were also observed in previous studies. It is known that low adherence to medications could lead to increased indirect costs in cardiovascular patients (Bansilal et al., 2015). Similarly, it has been found that nonadherent patients with bipolar disorder have increased indirect costs compared to adherent cohorts (Bagalman et al., 2010).

TABLE 3 | The impact of cost-related medication nonadherence on functional abilities among cancer survivors.

Variables	Activity limitation, OR (95% CI)[a]	Functional limitation, OR (95% CI)[a]	ADL limitation, OR (95%CI)[a]	IADL limitation, OR (95%CI)[a]
Cost-related medication nonadherence				
No	Ref	Ref	Ref	Ref
Yes	1.42 (1.25–1.60)	2.12 (1.81–2.49)	0.90 (0.73–1.11)	0.98 (0.83–1.16)
Age				
18–29	Ref	Ref	Ref	Ref
30–44	1.83 (1.23–2.72)	1.15 (0.82–1.63)	1.25 (0.49–3.20)	1.42 (0.73–2.78)
45–64	2.73 (1.88–3.95)	2.41 (1.73–3.36)	1.86 (0.76–4.58)	1.79 (0.97–3.29)
≥65	3.57 (2.46–5.18)	4.89 (3.52–6.81)	3.39 (1.38–8.31)	3.11 (1.70–5.70)
Gender				
Female	Ref	Ref	Ref	Ref
Male	0.93 (0.86–1.01)	1.54 (1.42–1.66)	1.26 (1.09–1.45)	1.38 (1.24–1.54)
Marital status				
Married	Ref	Ref	Ref	Ref
Non-married	1.57 (1.45–1.70)	1.13 (1.03–1.23)	1.41 (1.20–1.65)	2.02 (1.78–2.29)
Race				
Non-hispanic white	Ref	Ref	Ref	Ref
Non-hispanic black	0.91 (0.80–1.04)	0.82 (0.70–0.96)	1.15 (0.94–1.41)	0.94 (0.80–1.12)
Hispanic	0.76 (0.64–0.90)	0.77 (0.64–0.92)	1.42 (1.10–1.83)	0.96 (0.76–1.21)
Other[b]	0.94 (0.75–1.17)	0.76 (0.61–0.94)	1.61 (1.15–2.25)	1.48 (1.14–1.91)
Living region				
Northeast	Ref	Ref	Ref	Ref
North central/Midwest	1.13 (1.00–1.28)	1.22 (1.08–1.39)	0.87 (0.69–1.10)	1.00 (0.84–1.20)
South	1.02 (0.90–1.15)	1.10 (0.98–1.24)	0.88 (0.72–1.07)	0.84 (0.72–0.98)
West	1.28 (1.12–1.45)	1.17 (1.03–1.33)	1.06 (0.85–1.33)	1.06 (0.89–1.25)
Education				
Below high school	Ref	Ref	Ref	Ref
High school graduate	0.82 (0.73–0.92)	0.90 (0.77–1.05)	0.86 (0.70–1.05)	0.92 (0.79–1.07)
Above high school	0.86 (0.76–0.97)	0.85 (0.74–0.97)	0.77 (0.63–0.95)	0.94 (0.81–1.09)
Family income				
< $50,000	Ref	Ref	Ref	Ref
$50,000–$99,999	0.57 (0.52–0.63)	0.78 (0.70–0.86)	0.80 (0.66–0.98)	0.66 (0.57–0.77)
≥ $100,000	0.41 (0.36–0.47)	0.63 (0.56–0.71)	0.68 (0.50–0.93)	0.60 (0.48–0.75)
Health insurance				
No	Ref	Ref	Ref	Ref
Yes	0.91 (0.84–0.99)	0.97 (0.89–1.06)	1.14 (0.97–1.33)	1.06 (0.94–1.19)
BMI				
18.5–24.9	Ref	Ref	Ref	Ref
<18.5	1.63 (1.22–2.18)	1.26 (0.93–1.72)	1.89 (1.35–2.64)	2.09 (1.50–2.90)
25–29.9	0.97 (0.88–1.07)	1.34 (1.22–1.47)	0.82 (0.68–0.99)	0.87 (0.76–1.01)
≥30	1.22 (1.11–1.34)	2.07 (1.88–2.28)	1.02 (0.86–1.22)	1.04 (0.91–1.18)
Health status				
At least good	Ref	Ref	Ref	Ref
Poor or fair	2.76 (2.64–2.89)	2.25 (2.16–2.34)	3.06 (2.78–3.37)	2.72 (2.54–2.90)

ADL: activities of daily living; CI: Confidence interval; IADL: instrumental activities of daily living; OR: Odds ratio.

[a]*The results are weighted.*

[b]*Other includes Asian, Aleut, Alaskan Native, or American Indian, Pacific Islander, Hawaiian, Samoan, Guamanian, and multiple races.*

Increased productivity loss is another significantly associated outcome with cost-related medication nonadherence. In comparison with those without cost-related medication nonadherence, respondents with nonadherence were 28 and 46% more likely to have an increased work-loss day and bed disability day, respectively. Similar to economic burdens, more work-loss days and bed disability days could be associated with the poor clinical outcome of medication nonadherence. This is likely because of the fact that medication nonadherence would cause a worse clinical outcome in cancer survivors, which could further force them to take more "sick" days in comparison to adherent survivors (Chung et al., 2019). As mentioned above, medication nonadherence has shown to worsen the disease condition and to increase hospitalizations, thus, work-loss days and bed disability days would increase (Kaul et al., 2017).

Cost-related medication nonadherence in cancer survivors is also associated with activity limitation and functional limitation. Therefore, emphasizing cost-related adherence can help improve later quality of life outcomes and decrease the likelihood of limitations in everyday life. Healthcare providers and pharmacists could help in explaining the activity limitation and functional limitation that could occur with cost-related medication nonadherence. Providing patients with this information could shepherd them towards continuously and strictly following the guidelines of their prescriptions in an effort to avoid possible limitations and decreased quality of life.

It is important to emphasize medication adherence to cancer survivors. The results of this research can be used to highlight the importance of medication adherence for cancer survivors. When trying to prevent direct and indirect costs in relation to cost-related medication nonadherence, strategies to teach and inform cancer survivors of the financial importance of adhering to medication regimens can be extremely important in easing the possible long-term financial burden that is associated with cancer treatment. Healthcare providers could help implement strategies or interventions that educate a patient on the possible financial outcomes of cost-related medication nonadherence not only will improve a cancer survivors' financial situation, but also will improve the clinical outcome. Policymakers and third-party payers can help teach medication adherence to patients because it can help both of them save money. Since medication nonadherence is shown to increase hospitalizations and other healthcare visits, third-party payers like Medicare and Medicaid, as well as other policymakers, can highlight the savings related to medication adherence for cancer survivors, as it can also help save the third-party payers and policymakers money. In the end, there will always be financial burdens due to the high costs of cancer medications source from the background, so there should be a strong effort to decrease medication costs in order to improve medication adherence of both cancer survivors and other patients dealing with chronic illnesses.

To our knowledge, this study is the largest, most contemporary population-based analysis of the impact of cost-related medication nonadherence on economic burdens, productivity loss, and functional abilities among cancer survivors. Also, we used a nationally representative dataset to generalized the results to a national level. However, this study has several limitations. First, the measurement of dependent and independent variables was based on a self-report survey, which might cause recall biases in the results to a certain extent given that cancer survivors with worse functional abilities might have memory impairment or confusion when responding to survey questions. However, considering that productivity loss and limitations cannot be captured by claims data, survey data was the best source for the measurement of the outcomes in this study. Second, the survey did not do subgroup analyses for different cancer types. Cancer survivors with different types might have a different prevalence of cost-related medication nonadherence, and the impact of cost-related medication nonadherence might be different. Finally, because we used a cross-sectional study design, no conclusions on the casual inference between cost-related medication nonadherence and outcomes could be drawn.

CONCLUSION

Cancer survivors with cost-related medication nonadherence are more likely to have a higher economic burden and to have more productivity loss. In addition, cost-related medication nonadherence is associated with an increased probability of having activity limitation and functional limitation. The results highlight the need to draw increased attention to cost-related medication nonadherence among cancer survivors. Strategies are needed to help cancer survivors with cost-related medication nonadherence to be more adherent to prescriptions.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhis/index.htm.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of South Carolina. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KL, JY, and ML: concept and design. KL, XX, JB, and AH: acquisition, analysis, or interpretation of data. KL, XX, JB, AH, JY, and ML: drafting of the manuscript and critical revision of the manuscript for important intellectual content. KL and XX: statistical analysis. All authors contributed to the article and approved the submitted version.

REFERENCES

American Cancer Society (2019). *Cancer Treatment & Survivorship Facts & Figures 2019-2021*. Atlanta: American Cancer Society.

Bagalman, E., Yu-Isenberg, K. S., Durden, E., Crivera, C., Dirani, R., and Bunn, W. B. (2010). Indirect Costs Associated with Nonadherence to Treatment for Bipolar Disorder. *J. Occup. Environ. Med.* 52 (5), 478–485. doi:10.1097/jom.0b013e3181db811d

Bansilal, S., Castellano, J. M., and Fuster, V. (2015). Global burden of CVD: Focus on Secondary Prevention of Cardiovascular Disease. *Int. J. Cardiol.* 201, S1–S7. doi:10.1016/s0167-5273(15)31026-3

Baskar, R., Lee, K. A., Yeo, R., and Yeoh, K. W. (2012). Cancer and Radiation Therapy: Current Advances and Future Directions. *Int. J. Med. Sci.* 9 (3), 193–199. doi:10.7150/ijms.3635

Bouwman, L., Eeltink, C. M., Visser, O., Janssen, J. J. W. M., and Maaskant, J. M. (2017). Prevalence and Associated Factors of Medication Non-adherence in Hematological-Oncological Patients in Their home Situation. *BMC Cancer* 17 (1), 739. doi:10.1186/s12885-017-3735-1

Boyd, P., Lowry, M., Morris, K. L., Land, S. R., Agurs-Collins, T., Hall, K., et al. (2020). Health Behaviors of Cancer Survivors and Population Controls from the National Health Interview Survey (2005-2015). *JNCI Cancer Spectr.* 4 (5), pkaa043. doi:10.1093/jncics/pkaa043

Carlotto, A., Hogsett, V. L., Maiorini, E. M., Razulis, J. G., and Sonis, S. T. (2013). The Economic burden of Toxicities Associated with Cancer Treatment: Review of the Literature and Analysis of Nausea and Vomiting, Diarrhoea, Oral Mucositis and Fatigue. *Pharmacoeconomics* 31 (9), 753–766. doi:10.1007/s40273-013-0081-2

Chou, W. C., Chen, J.-S., Hung, C. Y., Lu, C. H., Shao, Y. Y., Chiou, T. J., et al. (2019). A Nationwide Survey of Adherence to Analgesic Drugs Among Cancer

Patients in Taiwan: Prevalence, Determinants, and Impact on Quality of Life. *Support Care Cancer* 27 (8), 2857–2867. doi:10.1007/s00520-018-4599-x

Chung, G. C., Marottoli, R. A., Cooney, L. M., and Rhee, T. G. (2019). Cost-Related Medication Nonadherence Among Older Adults: Findings from a Nationally Representative Sample. *J. Am. Geriatr. Soc.* 67 (12), 2463–2473. doi:10.1111/jgs.16141

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., and Garcia-Cardenas, V. (2018). Economic Impact of Medication Non-adherence by Disease Groups: a Systematic Review. *BMJ Open* 8 (1), e016982. doi:10.1136/bmjopen-2017-016982

Dee, E. C., Muralidhar, V., Butler, S. S., Yu, Z., Sha, S. T., Mahal, B. A., et al. (2020). General and Health-Related Internet Use Among Cancer Survivors in the United States: A 2013-2018 Cross-Sectional Analysis. *J. Natl. Compr. Canc Netw.* 18 (11), 1468–1475. doi:10.6004/jnccn.2020.7591

Dresden, S. M., Powell, E. S., Kang, R., McHugh, M., Cooper, A. J., and Feinglass, J. (2017). Increased Emergency Department Use in Illinois after Implementation of the Patient Protection and Affordable Care Act. *Ann. Emerg. Med.* 69 (2), 172–180. doi:10.1016/j.annemergmed.2016.06.026

Epstein, R. M., Duberstein, P. R., Fenton, J. J., Fiscella, K., Hoerger, M., Tancredi, D. J., et al. (2017). Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer: The VOICE Randomized Clinical Trial. *JAMA Oncol.* 3 (1), 92–100. doi:10.1001/jamaoncol.2016.4373

Fenn, K. M., Evans, S. B., McCorkle, R., DiGiovanna, M. P., Pusztai, L., Sanft, T., et al. (2014). Impact of Financial Burden of Cancer on Survivors' Quality of Life. *Jop* 10 (5), 332–338. doi:10.1200/jop.2013.001322

French, M. T., Homer, J., Gumus, G., and Hickling, L. (2016). Key Provisions of the Patient Protection and Affordable Care Act (ACA): A Systematic Review and Presentation of Early Research Findings. *Health Serv. Res.* 51 (5), 1735–1771. doi:10.1111/1475-6773.12511

Greenlee, H., Shi, Z., Sardo Molmenti, C. L., Rundle, A., and Tsai, W. Y. (2016). Trends in Obesity Prevalence in Adults with a History of Cancer: Results from the US National Health Interview Survey, 1997 to 2014. *Jco* 34 (26), 3133–3140. doi:10.1200/jco.2016.66.4391

Guy, G. P., Jr, Yabroff, K. R., Ekwueme, D. U., Rim, S. H., Li, R., and Richardson, L. C. (2017). Economic Burden of Chronic Conditions Among Survivors of Cancer in the United States. *Jco* 35 (18), 2053–2061. doi:10.1200/jco.2016.71.9716

Katz, S. (1983). Assessing Self-Maintenance: Activities of Daily Living, Mobility, and Instrumental Activities of Daily Living. *J. Am. Geriatr. Soc.* 31 (12), 721–727. doi:10.1111/j.1532-5415.1983.tb03391.x

Kaul, S., Avila, J. C., Mehta, H. B., Rodriguez, A. M., Kuo, Y.-F., and Kirchhoff, A. C. (2017). Cost-related Medication Nonadherence Among Adolescent and Young Adult Cancer Survivors. *Cancer* 123 (14), 2726–2734. doi:10.1002/cncr.30648

Mariotto, A. B., Robin Yabroff, K., Shao, Y., Feuer, E. J., and Brown, M. L. (2011). Projections of the Cost of Cancer Care in the United States: 2010-2020. *JNCI J. Natl. Cancer Inst.* 103 (2), 117–128. doi:10.1093/jnci/djq495

Martin, C. L., Tate, D. F., and Valle, C. G. (2018). Nonadherence to Daily Self-Weighing and Activity Tracking Is Associated with Weight Fluctuations Among African American Breast Cancer Survivors. *PLoS One* 13 (6), e0199751. doi:10.1371/journal.pone.0199751

Mechanic, D. (2014). More People Than Ever before Are Receiving Behavioral Health Care in the United States, but Gaps and Challenges Remain. *Health Aff.* 33 (8), 1416–1424. doi:10.1377/hlthaff.2014.0504

Meneses, K., Azuero, A., Hassey, L., McNees, P., and Pisu, M. (2012). Does Economic Burden Influence Quality of Life in Breast Cancer Survivors? *Gynecol. Oncol.* 124 (3), 437–443. doi:10.1016/j.ygyno.2011.11.038

Mirza, A. S., Pabbathi, S., Lu, Y., Ayoubi, N., Ewing, A., Jaglal, M., et al. (2018). Comorbidities, Risk, and Socioeconomic Factors of Uninsured Cancer Survivors. *Medicine (Baltimore)* 97 (47), e13121. doi:10.1097/md.0000000000013121

National Center for Health Statistics (2020). *National Health Interview Survey*. Atlanta, GA: US Department of Health and Human Services, CDC, National Center for Health Statistics. Available at: https://www.cdc.gov/nchs/nhis.htm.

Nekhlyudov, L., Madden, J., Graves, A. J., Zhang, F., Soumerai, S. B., and Ross-Degnan, D. (2011). Cost-Related Medication Nonadherence and Cost-Saving Strategies Used by Elderly Medicare Cancer Survivors. *J. Cancer Surviv* 5 (4), 395–404. doi:10.1007/s11764-011-0188-4

Parsons, V. L., Moriarity, C., Jonas, K., Moore, T. F., Davis, K. E., and Tompkins, L. (2014). Design and Estimation for the National Health Interview Survey, 2006-2015. *Vital Health Stat.* 2 (165), 1–53.

Sawaya, G. F., Sanstead, E., Alarid-Escudero, F., Smith-McCune, K., Gregorich, S. E., Silverberg, M. J., et al. (2019). Estimated Quality of Life and Economic Outcomes Associated with 12 Cervical Cancer Screening Strategies. *JAMA Intern. Med.* 179 (7), 867–878. doi:10.1001/jamainternmed.2019.0299

Shafrin, J., Sullivan, J., Chou, J. W., Neely, M. N., Doan, J. F., and Maclean, J. (2017). The Effect of Medication Nonadherence on Progression-free Survival Among Patients with Renal Cell Carcinoma. *Cmar* 9, 731–739. doi:10.2147/cmar.s148199

Siegel, R. L., Miller, K. D., and Jemal, A. (2019). Cancer Statistics, 2019. *CA A. Cancer J. Clin.* 69 (1), 7–34. doi:10.3322/caac.21551

Smith, G. L., Lopez-Olivo, M. A., Advani, P. G., Ning, M. S., Geng, Y., Giordano, S. H., et al. (2019). Financial Burdens of Cancer Treatment: A Systematic Review of Risk Factors and Outcomes. *J. Natl. Compr. Cancer Netw. JNCCN* 17 (10), 1184–1192. doi:10.6004/jnccn.2019.7305

Zhang, J. X., and Meltzer, D. O. (2015). Risk Factors for Cost-Related Medication Non-adherence Among Older Patients with Cancer. *Integr. Cancer Sci. Ther.* 2 (6), 300–304.

Zhao, J., Zheng, Z., Han, X., Davidoff, A. J., Banegas, M. P., Rai, A., et al. (2019). Cancer History, Health Insurance Coverage, and Cost-Related Medication Nonadherence and Medication Cost-Coping Strategies in the United States. *Value in Health* 22 (7), 762–767. doi:10.1016/j.jval.2019.01.015

Zhou, J., Han, J., Nutescu, E. A., Patel, P. R., Sweiss, K., and Calip, G. S. (2019). Discontinuation and Nonadherence to Medications for Chronic Conditions after Hematopoietic Cell Transplantation: A 6-Year Propensity Score-Matched Cohort Study. *Pharmacotherapy* 39 (1), 55–66. doi:10.1002/phar.2197

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The Efficacy of Pyrotinib as a Third- or Higher-Line Treatment in HER2-Positive Metastatic Breast Cancer Patients Exposed to Lapatinib Compared to Lapatinib-Naive Patients: A Real-World Study

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Background: Pyrotinib is a novel irreversible pan-ErbB receptor tyrosine kinase inhibitor. Evidence of the efficacy of pyrotinib-based treatments for HER2-positive metastatic breast cancer (MBC) in patients exposed to lapatinib is limited.

Methods: Ninety-four patients who received pyrotinib as a third- or higher-line treatment for HER2-positive MBC were included in this retrospective study. The primary and secondary endpoints were overall survival (OS) and progression-free survival (PFS). Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) analysis were implemented to balance important patient characteristics between groups.

Results: Thirty (31.9%) patients were pretreated with lapatinib and subsequently received pyrotinib as an anti-HER2 treatment, and 64 (68.1%) patients did not receive this treatment. The OS and PFS indicated a beneficial trend in lapatinib-naive group compared to lapatinib-treated group in either the original cohort (PFS: 9.02 vs 6.36 months, $p = 0.05$; OS: 20.73 vs 14.35 months, $p = 0.08$) or the PSM (PFS: 9.02 vs 6.08 months, $p = 0.07$; OS: 19.07 vs 18.00 months, $p = 0.61$) or IPTW (PFS: 9.90 vs 6.17 months, $p = 0.05$; OS: 19.53 vs 15.10 months, $p = 0.08$) cohorts. Subgroup analyses demonstrated lapatinib treatment-related differences in PFS in the premenopausal subgroup and the no prior trastuzumab treatment subgroup, but no significant differences were observed in OS.

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Conclusion: Pyrotinib-based therapy demonstrated promising effects in HER2-positive MBC patients in a real-world study, especially in lapatinib-naive patients, and also some activity in lapatinib-treated patients.

Keywords: pyrotinib, lapatinib-treated, lapatinib-naive, HER2 breast cancer, metastases

INTRODUCTION

Among patients with metastatic breast cancer (MBC), more than 20% have HER2-positive disease (Cobleigh et al., 2020; Howlader et al., 2014). Although this subtype of breast cancer has been historically associated with poor outcomes, the development of anti-HER2-targeted therapies has notably increased the median progression-free survival (PFS) and overall survival (OS) of patients (Slamon et al., 2001; Dawood et al., 2010; Swain et al., 2013; Mendes et al., 2015; Swain et al., 2015; Jain et al., 2018; Tripathy et al., 2020). Currently, tyrosine kinase inhibitors (TKIs) are officially approved by the International and Chinese Food and Drug Administrations for HER2-positive recurrence and MBC as second- or higher-line treatments (Ryan et al., 2008; Deeks, 2017; Blair, 2018).

Four TKIs are used to treat HER2-positive MBC, namely, lapatinib, tucatinib, neratinib, and pyrotinib (Xuhong et al., 2019; Lee, 2020). All of them were pan-ErbB receptors TKIs except tucatinib, which was a single HER2-targeted TKI (Wong et al., 2009; Awada et al., 2016; Li et al., 2017; Lin et al., 2020). Clinical trial results and our previous real-world study indicated that pyrotinib plus capecitabine had significantly superior efficacy and resulted in greater PFS than lapatinib combined with capecitabine (Jiang et al., 2019; Ma et al., 2019; Chen et al., 2020; Xuhong et al., 2020; Xu et al., 2021). Pyrotinib also demonstrated promising effects in brain metastatic HER2-positive breast cancer regardless of whether patients were previously treated with trastuzumab (Ma et al., 2019; (Anwar et al., 2021). The TBCRC022 study indicated that neratinib plus capecitabine was effective in HER2-positive patients with brain metastasis of breast cancer among the lapatinib-treated group (Freedman et al., 2019). However, whether pyrotinib is effective in patients after lapatinib treatment remains controversial (Lin et al., 2020; Song et al., 2020). This study was conducted after obtaining our final follow-up data to evaluate the effectiveness of pyrotinib as a third- or higher-line treatment. The aim of the study is to report the results of pyrotinib therapy in patients with and without prior lapatinib exposure before and after propensity score matching (PSM) analysis and inverse probability of treatment weighting (IPTW) analysis, with the hope of providing evidence of the effectiveness of pyrotinib-based treatment after failure of lapatinib-treated therapy.

METHODS

Patient Eligibility and Data Collection

One hundred sixty-eight female patients with HER2-positive MBC were enrolled from June 2018 to August 2019. The follow-up period of the present study lasted until December 2020. Among these patients, 94 were treated with pyrotinib as a third- or higher-line treatment. Thirty (31.9%) patients had previously been treated with lapatinib and subsequently received pyrotinib-based therapy, and 64 (68.1%) patients had not been treated with lapatinib in this retrospective, multicenter, real-world study. Using PSM, a total of 60 patients (24 lapatinib-treated patients (40.0%) versus 36 lapatinib-naive patients (60.0%)) were matched, and the two groups were confirmed to have similar baseline clinical data ($p > 0.05$). Pyrotinib treatment was identical to that in our previous study (Geyer et al., 2006; Cameron et al., 2010; Xu et al., 2011) (**Figure 1**). The inclusion criteria were as follows (Cobleigh et al., 2020): confirmed HER2 positivity by immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH) according to the HER2 status testing guidelines (Wolff et al., 2018; Howlader et al., 2014) stable vital signs and adequate physiological function (heart, liver, and kidney); and (Tripathy et al., 2020) a measurable lesion. The exclusion criteria were as follows (Cobleigh et al., 2020): discontinued pyrotinib treatment (Howlader et al., 2014); pyrotinib use in a neoadjuvant therapy setting (Tripathy et al., 2020); severe adverse side effects could not be controlled by dose reduction or adjuvant medication; and (Dawood et al., 2010) dropped out for other unknown reasons.

The pyrotinib treatment stage was defined as follows: first-line treatment was defined as the treatment of a patient with *de novo* stage IV breast cancer who was not treated previously with anti-HER2 medications or treatment of a patient with recurrence >12 months after discontinuation of trastuzumab. Second-line treatment was administered to patients with recurrence within 12 months of discontinuation of trastuzumab, recurrence during adjuvant therapy with trastuzumab, or progression following first-line treatment. Third- or higher-line treatment was administered to patients with progression or recurrence following second-line treatment and for whom any one of the anti-HER2 or chemotherapeutic drugs had been changed.

All patients and/or their immediate families understood and consented to participate in this study and provided written informed consent for clinical data access, scheduled follow-up, and survival analysis. The Ethics Committee of the Second Xiangya Hospital of Central South University reviewed and approved the study.

Endpoint Definition and Assessments

OS, the primary endpoint of our study, was defined as the time from enrollment until death due to any cause or the latest date the patient was known to be alive. The secondary endpoint, PFS, was defined as the time from drug administration to death or disease progression (whichever occurred first). For patients without OS/PFS events, the follow-up information was estimated by each center's staff based on the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criterion. Each patient underwent a 14- to 21-day clinical follow-up schedule and 2 to 3 drug cycles (6–9 weeks) of imaging follow-up (computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, PET/CT scan, and bone scan) after the beginning of pyrotinib treatment until the primary endpoint was reached.

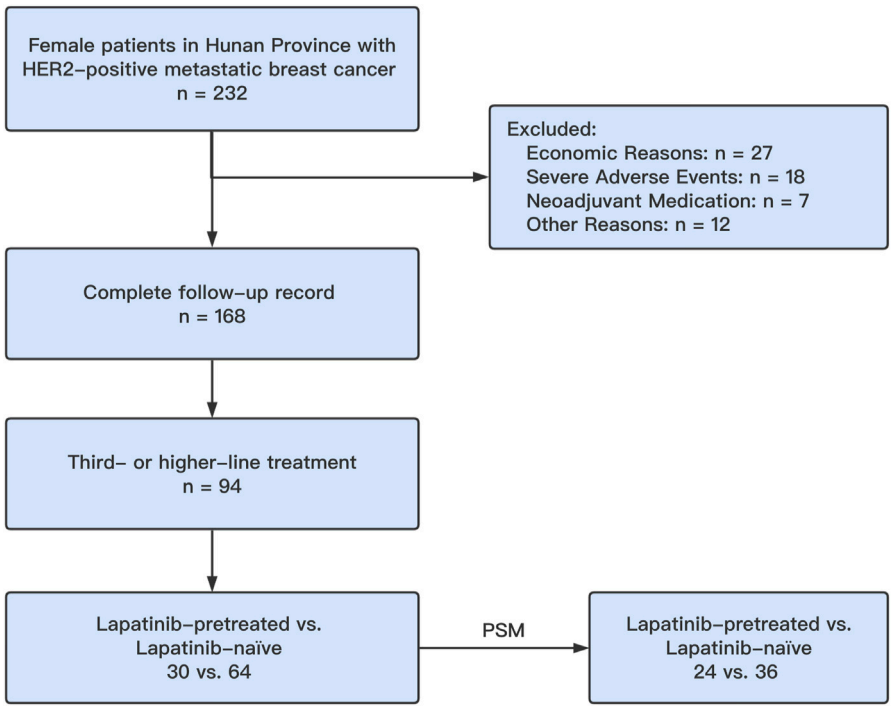


FIGURE 1 | CONSORT diagram for patient selection for the study. PSM, propensity score matching.

Propensity Score Matching and Inverse Probability of Treatment Weighting

The critical covariate (metastatic site) exhibited heterogeneity between the lapatinib-treated and lapatinib-naive groups (**Table 1**), possibly affecting the outcomes from a clinical perspective. To balance the heterogeneous characteristics between the two groups, we implemented PSM using the R package "MatchIt" version 4.1.0 with the following settings: 1:2 pairing, nearest-neighbor methods, and a caliper of 0.02 (Pattanayak et al., 2011). After PSM, all categories were comparable (**Table 1**). Inverse probability of treatment weighting-adjusted (IPTW-adjusted) survival analysis was applied to reduce the differences in baseline variables.

Statistical Analyses

Pearson's chi-squared test or Fisher's exact test was utilized to assess the heterogeneity of categorical variables among the lapatinib-treated and lapatinib-naive groups. Survival curves for OS and PFS were constructed using the Kaplan–Meier methodology, and the distribution was estimated using the log-rank test. Median OS times and PFS were calculated and reported. Hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS were computed using a univariable Cox proportional hazards regression model (using the R package "survminer") and are presented as Forrest plots (using the R package "forestplot"). Statistical analyses and data visualization were performed using R (https://www.r-project.org/version 4.0.3) and RStudio (R-Studio Inc., Boston, United States version 1.3.1056). A p-value of less than 0.05 indicated statistical significance.

RESULTS

Baseline Characteristics

Of 94 eligible patients, the median age of the 94 patients was 48.5 years (range 28–71 years). Ninety (95.7%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Most patients were treated with pyrotinib plus capecitabine and had prior trastuzumab treatment. In the lapatinib-naive cohort, 44 (68.8%) patients were with lung and/or liver metastasis, 33 (51.6%) were ≥50 years old, and 34 (53.1%) had a premenopausal status. The hormone receptor status was similar between groups. The PSM cohort showed similar but more balanced patient characteristics than those in the initial cohort. The baseline clinical features of the patients before and after PSM are summarized in **Table 1**. The median PFS time of the patients was 7.54 months (95% CI 6.67–10.67 months), and the median OS time was 18.67 months (95% CI 14.97–24.47 months) (**Supplementary Figure S1**).

Patient Outcomes After Changing Tyrosine Kinase Inhibitor Treatment

The numbers of PFS events in the lapatinib-naive group were 51/64 (before PSM) and 27/36 (after PSM), and the numbers of OS events were 36/64 and 21/36, respectively. In the lapatinib-treated group, the numbers of PFS events were 28/30 (before PSM) and 22/24 (after PSM), and the numbers of OS events were 21/30 and 15/24, respectively. Kaplan–Meier survival curves for OS and PFS were constructed to compare the survival distribution according

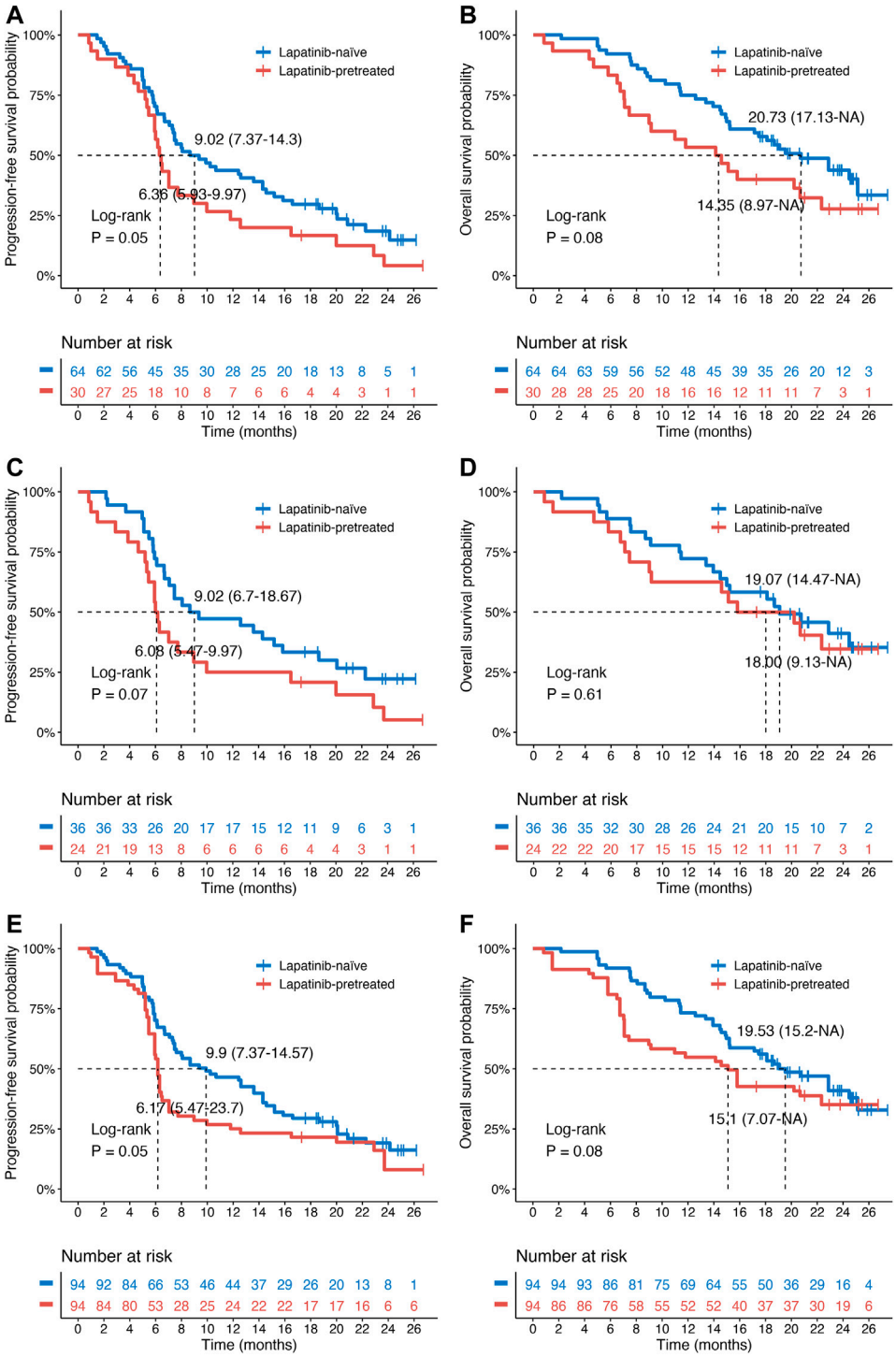
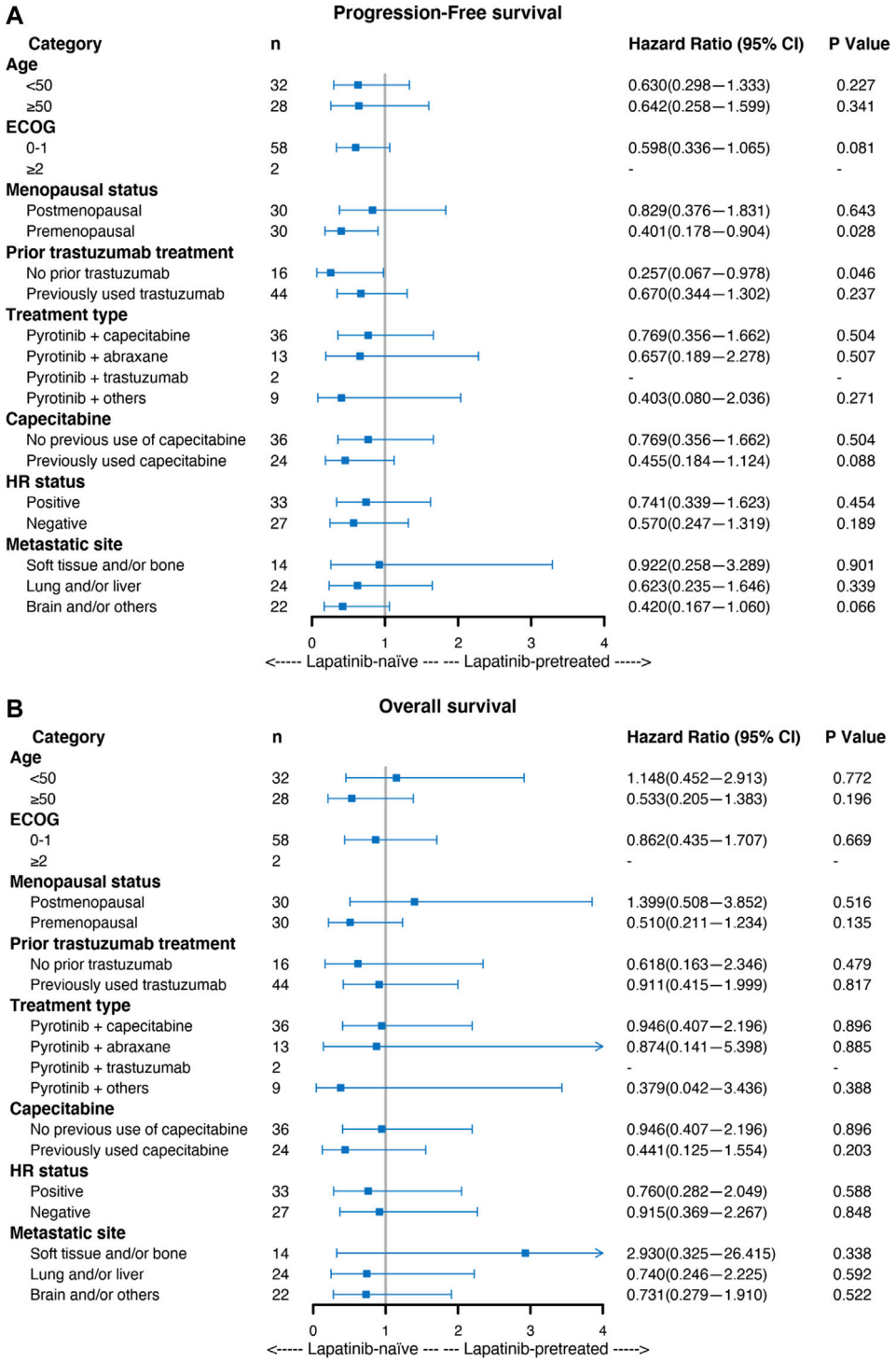


FIGURE 2 | Kaplan–Meier survival curves for patients with HER2-positive MBC treated with pyrotinib as a third- or higher-line treatment. **(A,B)** Progression-free survival (PFS)/overall survival (OS) of lapatinib-naive (*n* = 64) and lapatinib-treated (*n* = 30) patients in the original cohort. **(C,D)** PFS/OS of lapatinib-naive (*n* = 36) and lapatinib-treated (*n* = 24) patients in the PSM cohort. **(E,F)** PFS/OS of lapatinib-naive (*n* = 94) and lapatinib-treated (*n* = 94) patients in the IPTW-adjusted cohort. The *p*-values were determined by univariate log-rank tests. PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

to previous lapatinib treatment (**Figure 2**). The PFS and OS of the lapatinib-naive group were 43.8 and 75.0% at 12 months and 29.7% and 57.8% at 18 months, respectively. Comparatively, the PFS and OS of the lapatinib-treated group were 23.3 and 53.3% at 12 months and 16.7% and 40.0% at 18 months, respectively. The log-rank test results indicated a beneficial trend in the



lapatinib-naive group compared to the lapatinib-treated group in terms of PFS (9.02 (7.37–14.30) vs 6.36 (5.93–9.97) p = 0.05, **Figure 2A**) and OS (20.73 (17.13–NA) vs 14.35 (8.97–NA) p = 0.08, **Figure 2B**). We also confirmed this finding by performing analysis between the two groups in terms of PFS (9.02 (6.70–18.67) vs 6.08 (5.47–9.97) p = 0.07, **Figure 2C**) and OS (19.07 (14.47–NA) vs 18.00 (9.13–NA) p = 0.61, **Figure 2D**) in the PSM cohort and in IPTW-adjusted cohort (PFS: 9.90

TABLE 1 | Characteristics of patients who received pyrotinib as third- or higher-line therapy who previously were or were not treated with lapatinib.

Category	Before PSM			After PSM		
	Lapatinib-naive	Lapatinib-treated	*p*-Value	Lapatinib-naive	Lapatinib-treated	*p*-Value
	No. (%)	No. (%)		No. (%)	No. (%)	
Age						
<50	31 (48.4)	18 (60.0)	0.377	17 (47.2)	15 (62.5)	0.369
≥50	33 (51.6)	12 (40.0)		19 (52.8)	9 (37.5)	
ECOG Scale						
0–1	63 (98.4)	27 (90.0)	0.181	35 (97.2)	23 (95.8)	1.000
≥2	1 (1.6)	3 (10.0)		1 (2.8)	1 (4.2)	
Menopausal Status						
Postmenopausal	30 (46.9)	17 (56.7)	0.507	17 (47.2)	13 (54.2)	0.792
Premenopausal	34 (53.1)	13 (43.3)		19 (52.8)	11 (45.8)	
HR Status						
Positive	37 (57.8)	16 (53.3)	0.853	20 (55.6)	13 (54.2)	1.000
Negative	27 (42.2)	14 (46.7)		16 (44.4)	11 (45.8)	
Prior trastuzumab treatment						
No prior trastuzumab	19 (29.7)	5 (16.7)	0.273	12 (33.3)	4 (16.7)	0.258
Previous use of trastuzumab	45 (70.3)	25 (83.3)		24 (66.7)	20 (83.3)	
Treatment type						
Pyrotinib + Capecitabine	45 (70.3)	16 (53.3)	0.102	24 (66.7)	12 (50.0)	0.330
Pyrotinib + Abraxane	12 (18.8)	5 (16.7)		8 (22.2)	5 (20.8)	
Pyrotinib + Trastuzumab	2 (3.1)	1 (3.3)		1 (2.8)	1 (4.2)	
Pyrotinib + Others	5 (7.8)	8 (26.7)		3 (8.3)	6 (25.0)	
Metastatic Site						
Soft tissue and/or bone	9 (14.1)	5 (16.7)	<0.001	9 (25.0)	5 (20.8)	0.480
Lung and/or liver	44 (68.8)	8 (26.7)		16 (44.4)	8 (33.3)	
Brain and/or others	11 (17.2)	17 (56.7)		11 (30.6)	11 (45.8)	
Total	**64**	**30**		**36**		**24**

Abbreviations: *PSM, propensity score matching; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor.*

(7.37–14.57) vs 6.17 (5.47–23.70) $p = 0.05$, **Figure 2E**, and OS: 19.53 (15.20–NA) vs 15.10 (7.07–NA) $p = 0.08$, **Figure 2F**).

In the lapatinib-naive cohort, 24 patients (37.5%) achieved a partial response (PR), and two patients (3.10%) achieved a complete response (CR), resulting in an objective response rate (ORR) of 40.60%. In the lapatinib-treated cohort, 11 patients (36.70%) achieved a PR, and one patient (3.30%) achieved a CR, resulting in an ORR of 40.00%.

Subgroup Analysis

A subgroup analysis was performed to investigate the effect of previous lapatinib treatment on PFS and OS. Forest plots of the subgroup analysis are shown in **Figure 3**.

Univariable Cox analysis including the lapatinib-treated and lapatinib-naive groups showed similar outcomes. Most subgroups showed no significant difference in PFS (**Figure 3A**), except for the premenopausal subgroup (HR = 0.401, 95% CI 0.178–0.904, $p = 0.028$) and the subgroup without previous use of trastuzumab (HR = 0.257, 95% CI 0.067–0.978, $p = 0.046$). Similarly, no significant differences were found in OS in any subgroup analyses (**Figure 3B**).

DISCUSSION

HER2-positive MBC has a poor prognosis and a short survival time (4). Only 13.2% of patients survive for more than 5 years if they do not receive treatments that target HER2(4). Conversely, the continuous development and widespread use of anti-HER2 drugs such as trastuzumab (Slamon et al., 2001; Burstein et al., 2007; Robert et al., 2006), pertuzumab (Baselga et al., 2012), TDM1 (Verma et al., 2012), and lapatinib (Geyer et al., 2006; Cameron et al., 2010; Xu et al., 2011) have significantly prolonged the median survival time of HER2-positive MBC patients. Moreover, China has recently authorized the use of pyrotinib for HER2-positive MBC patients.

Lapatinib and pyrotinib are both small molecule TKIs. Lapatinib reversibly inhibits HER1 and HER2, while pyrotinib inhibits HER1, HER2, and HER4 (Ma et al., 2017; Li et al., 2019). The curative effect of pyrotinib is stronger than that of lapatinib because of the conjugated double bond structure (Ma et al., 2017; Li et al., 2019). Previous randomized controlled trials on pyrotinib have not included lapatinib-treated patients, resulting in a lack of evidence to guide practice for follow-up treatment after lapatinib failure. In this study, 24 patients were considered to be lapatinib-treated after PSM analysis, which resulted in an ORR of 40.0% and median PFS of 6.08 months. Furthermore, IPTW analysis showed 6.17 months of PFS in patients who were exposed to lapatinib previously. We compared our results with those of two other real-world studies. Lin et al. (2020) and Song et al. (2020) reported median PFS times of 5.4 months (ORR 23.2%) and 7.9 months (ORR 22.2%), respectively. Our results showed a median PFS of 9.02 months (PSM analysis) and 9.90 months (IPTW analysis) in the lapatinib-naive group, which was better than that from Lin's study (9.0 months) and Song's study (7.2 months). The differences between the studies of Lin and Song may be due to selection bias. To minimize this bias, our study assessed the efficacy of pyrotinib by applying a PSM and IPTW approach. Additionally, our results first revealed the OS of pyrotinib-based therapy, with survival times of 19.07 and 18.00 months (PSM analysis) and 19.53 and 15.10 months (IPTW analysis) for the lapatinib-naive and lapatinib-treated groups, respectively. Therefore, our study suggested that pyrotinib is still effective in patients who have lapatinib treatment failure.

Another TKI neratinib also showed good therapeutic effects (Geyer et al., 2006; Cameron et al., 2010; Xu et al., 2011). The NALA study reported median PFS times of 8.8 months in the neratinib plus capecitabine group and 6.6 months in the lapatinib plus capecitabine group (Geyer et al., 2006; Cameron et al., 2010; Xu et al., 2011), and the NEfERT-T trial reported a PFS time of 12.9 months in the neratinib plus paclitaxel group (Geyer et al., 2006; Cameron et al., 2010; Xu et al., 2011), suggesting that the curative effect of neratinib is stronger than that of lapatinib. Among patients treated with neratinib, the PFS time was 3.1 months for those previously treated with lapatinib, and the PFS time was and 5.5 months in the lapatinib-naive cohort (Freedman et al., 2019). Thus, this finding indicated that the therapeutic effect of pyrotinib in lapatinib-naive patients has a similar beneficial trend to that of neratinib. Therefore, giving priority to pyrotinib treatment may increase survival benefits, but more detailed clinical studies are needed in the future.

Our study was retrospective, and thus, the groups could not be prospectively randomized; therefore, it was subject to limitations, including a lack of some clinical factors, such as combined treatment, and possible selection bias. The sample size should be further expanded in clinical randomized controlled studies.

In conclusion, pyrotinib-based therapy exhibited potential effects on HER2-positive MBC patients in a real-world study, regardless of whether lapatinib treatment was previously administered or not. Particularly for patients without lapatinib exposure, they seemed to benefit more from pyrotinib-based therapy, reaching a better prognosis, which still awaits more solidate verification.

DATA AVAILABILITY STATEMENT

The code and datasets analyzed during the present study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA and QC collected and compiled the patients' information. DO and QC performed the literature search, data extraction, and statistical analysis and drafted the manuscript. WY and SW

designed and supervised the study. Other authors administered clinical therapy to patients and obtained patient follow-up information. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.682568/full#supplementary-material

REFERENCES

Anwar, M., Chen, Q., Ouyang, D., Wang, S., Xie, N., Ouyang, Q., et al. (2021). Pyrotinib Treatment in Patients with HER2-Positive Metastatic Breast Cancer and Brain Metastasis: Exploratory Final Analysis of Real-World, Multicenter Data. *Clin Cancer Res.* doi:10.1158/1078-0432.ccr-21-0474

Awada, A., Colomer, R., Inoue, K., Bondarenko, I., Badwe, R. A., Demetriou, G., et al. (2016). Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer. *JAMA Oncol.* 2 (12), 1557–1564. doi:10.1001/jamaoncol.2016.0237

Baselga, J., Cortés, J., Kim, S.-B., Im, S.-A., Hegg, R., Im, Y.-H., et al. (2012). Pertuzumab Plus Trastuzumab Plus Docetaxel for Metastatic Breast Cancer. *N. Engl. J. Med.* 366 (2), 109–119. doi:10.1056/nejmoa1113216

Blair, H. A. (2018). Pyrotinib: First Global Approval. *Drugs* 78 (16), 1751–1755. doi:10.1007/s40265-018-0997-0

Burstein, H. J., Keshaviah, A., Baron, A. D., Hart, R. D., Lambert-Falls, R., Marcom, P. K., et al. (2007). Trastuzumab Plus Vinorelbine or Taxane Chemotherapy for HER2-Overexpressing Metastatic Breast Cancer: the Trastuzumab and Vinorelbine or Taxane Study. *Cancer* 110 (5), 965–972. doi:10.1002/cncr.22885

Cameron, D., Casey, M., Oliva, C., Newstat, B., Imwalle, B., and Geyer, C. E. (2010). Lapatinib Plus Capecitabine in Women with HER-2-Positive Advanced Breast Cancer: Final Survival Analysis of a Phase III Randomized Trial. *The oncologist* 15 (9), 924–934. doi:10.1634/theoncologist.2009-0181

Chen, Q., Ouyang, D., Anwar, M., Xie, N., Wang, S., Fan, P., et al. (2020). Effectiveness and Safety of Pyrotinib, and Association of Biomarker with Progression-free Survival in Patients with HER2-Positive Metastatic Breast Cancer: A Real-World, Multicentre Analysis. *Front. Oncol.* 10, 811. doi:10.3389/fonc.2020.00811

Cobleigh, M., Yardley, D. A., Brufsky, A. M., Rugo, H. S., Swain, S. M., Kaufman, P. A., et al. (2020). Baseline Characteristics, Treatment Patterns, and Outcomes in Patients with HER2-Positive Metastatic Breast Cancer by Hormone Receptor Status from SystHERs. *Clin. Cancer Res.* 26 (5), 1105–1113. doi:10.1158/1078-0432.ccr-19-2350

Dawood, S., Broglio, K., Buzdar, A. U., Hortobagyi, G. N., and Giordano, S. H. (2010). Prognosis of Women with Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: an Institutional-Based Review. *Jco* 28 (1), 92–98. doi:10.1200/jco.2008.19.9844

Deeks, E. D. (2017). Neratinib: First Global Approval. *Drugs* 77 (15), 1695–1704. doi:10.1007/s40265-017-0811-4

Freedman, R. A., Gelman, R. S., Anders, C. K., Melisko, M. E., Parsons, H. A., Cropp, A. M., et al. (2019). TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. *J. Clin. Oncol.* 37 (13), 1081–1089. doi:10.1200/JCO.18.01511

Geyer, C. E., Forster, J., Lindquist, D., Chan, S., Romieu, C. G., Pienkowski, T., et al. (2006). Lapatinib Plus Capecitabine for HER2-Positive Advanced Breast Cancer. *N. Engl. J. Med.* 355 (26), 2733–2743. doi:10.1056/nejmoa064320

Howlader, N., Altekruse, S. F., Li, C. I., Chen, V. W., Clarke, C. A., Ries, L. A., et al. (2014). US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status. *J. Natl. Cancer Inst.* 106 (5). doi:10.1093/jnci/dju055

Jain, S., Shah, A. N., Santa-Maria, C. A., Siziopikou, K., Rademaker, A., Helenowski, I., et al. (2018). Phase I Study of Alpelisib (BYL-719) and Trastuzumab Emtansine (T-DM1) in HER2-Positive Metastatic Breast Cancer (MBC) after Trastuzumab and Taxane Therapy. *Breast Cancer Res. Treat.* 171 (2), 371–381. doi:10.1007/s10549-018-4792-0

Jiang, Z., Yan, M., Hu, X., Zhang, Q., Ouyang, Q., Feng, J., et al. (2019). Pyrotinib Combined with Capecitabine in Women with HER2+ Metastatic Breast Cancer Previously Treated with Trastuzumab and Taxanes: A Randomized Phase III Study. *Jco* 37, 1001. doi:10.1200/jco.2019.37.15_suppl.1001

Lee, A. (2020). Tucatinib: First Approval. *Drugs* 80 (10), 1033–1038. doi:10.1007/s40265-020-01340-w

Li, Q., Guan, X., Chen, S., Yi, Z., Lan, B., Xing, P., et al. (2019). Safety, Efficacy, and Biomarker Analysis of Pyrotinib in Combination with Capecitabine in HER2-Positive Metastatic Breast Cancer Patients: A Phase I Clinical Trial. *Clin. Cancer Res.* 25 (17), 5212–5220. doi:10.1158/1078-0432.ccr-18-4173

Li, X., Yang, C., Wan, H., Zhang, G., Feng, J., Zhang, L., et al. (2017). Discovery and Development of Pyrotinib: A Novel Irreversible EGFR/HER2 Dual Tyrosine Kinase Inhibitor with Favorable Safety Profiles for the Treatment of Breast Cancer. *Eur. J. Pharm. Sci.* 110, 51–61. doi:10.1016/j.ejps.2017.01.021

Lin, Y., Lin, M., Zhang, J., Wang, B., Tao, Z., Du, Y., et al. (2020). Real-World Data of Pyrotinib-Based Therapy in Metastatic HER2-Positive Breast Cancer:

Promising Efficacy in Lapatinib-Treated Patients and in Brain Metastasis. *Cancer Res. Treat.* 52 (4), 1059–1066. doi:10.4143/crt.2019.633

Ma, F., Li, Q., Chen, S., Zhu, W., Fan, Y., Wang, J., et al. (2017). Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in Patients with Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *Jco* 35 (27), 3105–3112. doi:10.1200/jco.2016.69.6179

Ma, F., Ouyang, Q., Li, W., Jiang, Z., Tong, Z., Liu, Y., et al. (2019). Pyrotinib or Lapatinib Combined with Capecitabine in HER2-Positive Metastatic Breast Cancer with Prior Taxanes, Anthracyclines, And/or Trastuzumab: A Randomized, Phase II Study. *Jco* 37 (29), 2610–2619. doi:10.1200/jco.19.00108

Mendes, D., Alves, C., Afonso, N., Cardoso, F., Passos-Coelho, J. L., Costa, L., et al. (2015). The Benefit of HER2-Targeted Therapies on Overall Survival of Patients with Metastatic HER2-Positive Breast Cancer-Aa Systematic Review. *Breast Cancer Res. : BCR* 17, 140. doi:10.1186/s13058-015-0648-2

Pattanayak, C. W., Rubin, D. B., and Zell, E. R. (2011). Propensity Score Methods for Creating Covariate Balance in Observational Studies. *Revista Española de Cardiología (English Edition)* 64 (10), 897–903. doi:10.1016/j.rec.2011.06.008

Robert, N., Leyland-Jones, B., Asmar, L., Belt, R., Ilegbodu, D., Loesch, D., et al. (2006). Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared with Trastuzumab and Paclitaxel in Women with HER-2-Overexpressing Metastatic Breast Cancer. *Jco* 24 (18), 2786–2792. doi:10.1200/jco.2005.04.1764

Ryan, Q., Ibrahim, A., Cohen, M. H., Johnson, J., Ko, C. w., Sridhara, R., et al. (2008). FDA Drug Approval Summary: Lapatinib in Combination with Capecitabine for Previously Treated Metastatic Breast Cancer that Overexpresses HER-2. *Oncol.* 13 (10), 1114–1119. doi:10.1634/theoncologist.2008-0816

Saura, C., Oliveira, M., Feng, Y.-H., Dai, M.-S., Chen, S.-W., Hurvitz, S. A., et al. (2020). Neratinib Plus Capecitabine versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated with ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. *Jco* 38 (27), 3138–3149. doi:10.1200/jco.20.00147

Slamon, D. J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., et al. (2001). Use of Chemotherapy Plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer that Overexpresses HER2. *N. Engl. J. Med.* 344 (11), 783–792. doi:10.1056/nejm200103153441101

Song, G. H., Li, H. P., Di, L. J., Yan, Y., Jiang, H. F., Xu, L., et al. (2020). [Efficacy and Safety of Oral Pyrotinib in HER2 Positive Metastatic Breast Cancer: Real-World Practice]. *Beijing Da Xue Xue Bao Yi Xue Ban* 52 (2), 254–260.

Swain, S. M., Baselga, J., Kim, S.-B., Ro, J., Semiglazov, V., Campone, M., et al. (2015). Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. *N. Engl. J. Med.* 372 (8), 724–734. doi:10.1056/nejmoa1413513

Swain, S. M., Kim, S.-B., Cortés, J., Ro, J., Semiglazov, V., Campone, M., et al. (2013). Pertuzumab, Trastuzumab, and Docetaxel for HER2-Positive Metastatic Breast Cancer (CLEOPATRA Study): Overall Survival Results from a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study. *Lancet Oncol.* 14 (6), 461–471. doi:10.1016/s1470-2045(13)70130-x

Tripathy, D., Brufsky, A., Cobleigh, M., Jahanzeb, M., Kaufman, P. A., Mason, G., et al. (2020). De Novo Versus Recurrent HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from the SystHERs Registry. *Oncol.* 25 (2), e214–e22. doi:10.1634/theoncologist.2019-0446

Verma, S., Miles, D., Gianni, L., Krop, I. E., Welslau, M., Baselga, J., et al. (2012). Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *N. Engl. J. Med.* 367 (19), 1783–1791. doi:10.1056/nejmoa1209124

Wolff, A. C., Hammond, M. E. H., Allison, K. H., Harvey, B. E., Mangu, P. B., Bartlett, J. M. S., et al. (2018). Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch. Pathol. Lab. Med.* 142 (11), 1364–1382. doi:10.5858/arpa.2018-0902-sa

Wong, K.-K., Fracasso, P. M., Bukowski, R. M., Lynch, T. J., Munster, P. N., Shapiro, G. I., et al. (2009). A Phase I Study with Neratinib (HKI-272), an Irreversible pan ErbB Receptor Tyrosine Kinase Inhibitor, in Patients with Solid Tumors. *Clin. Cancer Res.* 15 (7), 2552–2558. doi:10.1158/1078-0432.ccr-08-1978

Xu, B.-H., Jiang, Z.-F., Chua, D., Shao, Z.-M., Luo, R.-C., Wang, X.-J., et al. (2011). Lapatinib Plus Capecitabine in Treating HER2-Positive Advanced Breast Cancer: Efficacy, Safety, and Biomarker Results from Chinese Patients. *Chin. J. Cancer* 30 (5), 327–335. doi:10.5732/cjc.010.10507

Xu, B., Yan, M., Ma, F., Hu, X., Feng, J., Ouyang, Q., et al. (2021). Pyrotinib Plus Capecitabine versus Lapatinib Plus Capecitabine for the Treatment of HER2-Positive Metastatic Breast Cancer (PHOEBE): a Multicentre, Open-Label, Randomised, Controlled, Phase 3 Trial. *Lancet Oncol.* 22 (3), 351–360. doi:10.1016/s1470-2045(20)30702-6

Xuhong, J., Qi, X., Tang, P., Fan, L., Chen, L., Zhang, F., et al. (2020). Neoadjuvant Pyrotinib Plus Trastuzumab and Chemotherapy for Stage I-III HER2-Positive Breast Cancer: A Phase II Clinical Trial. *The oncologist* 25 (12), e1909–e20. doi:10.1002/onco.13546

Xuhong, J. C., Qi, X. W., Zhang, Y., and Jiang, J. (2019). Mechanism, Safety and Efficacy of Three Tyrosine Kinase Inhibitors Lapatinib, Neratinib and Pyrotinib in HER2-Positive Breast Cancer. *Am. J. Cancer Res.* 9 (10), 2103–2119.

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Treatment for Severe Lupus Nephritis: A Cost-Effectiveness Analysis in China

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Background: Lupus nephritis (LN) is the most common secondary glomerular diseases that will cause end-stage renal disease (ESRD) and renal-related death. The cost-effectiveness of various treatments for LN recommended by official guidelines has not been investigated in China. Our study is to evaluate clinical prognosis and cost-effectiveness of the current treatments for severe LN.

Methods: A Markov model was simulated for 1,000 LN patients of 30 years old, over a 3-years and 30-years lifetime horizon respectively. We assessed the cost-effectiveness of six therapeutic strategies from a societal perspective, with cyclophosphamide (CYC) or mycophenolate mofetil (MMF) induction therapy followed by CYC, MMF or azathioprine (AZA) maintenance therapy. Main outcomes included quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER) and clinical prognosis. One and three times gross domestic product (GDP) per capita were used as the willingness-to-pay (WTP) thresholds. We also carried out sensitivity analysis under a lifetime horizon.

Results: Compared with the baseline strategy of CYC induction and maintenance, for a 3-years horizon the most cost-effective strategy was CYC induction and AZA maintenance with $448 per QALY gained, followed by MMF induction and AZA maintenance which however was not cost-effective under the one times GDP per capita WTP threshold. For a lifetime horizon, CYC induction and AZA maintenance remained the most cost-effective strategy but MMF induction and maintenance became cost-effective under the one times GDP per capita WTP threshold and achieved a higher complete remission rate (57.2 versus 48.9%) and lower risks of ESRD (3.3 versus 5.8%) and all-cause mortality (36.0 versus 40.8%). The risk of developing ESRD during maintenance was the most influential parameter affecting ICER.

Conclusions: The strategy of CYC induction followed by AZA maintenance was the most cost-effective strategy in China for short-term treatment, while the strategy of MMF in both induction and maintenance became cost-effective and yielded more desirable clinical outcomes for lifetime treatment. The uncertainty analysis supported the need for monitoring the progression to ESRD.

Keywords: Cost-Effectiveness, severe lupus nephritis, Markov model, therapeutic strategies, clinical prognosis

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INTRODUCTION

Lupus nephritis (LN) is a common complication of systemic lupus erythematosus (SLE), a chronic inflammatory disease that may induce organ damage, typically the kidney. The frequency of developing LN from SLE varies worldwide, with 40–80% among Asians (Almaani et al., 2017). In China, LN has become the most common secondary glomerular diseases, accounting for over 50% of adults with SLE (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019). The standardized mortality ratio of LN patients was around six compared with the general population (Yap et al., 2012; Parikh et al., 2020). 10% of LN patients developed end-stage renal disease (ESRD) and mortality due to kidney disease was found to be 5–25% for patients with proliferative LN (Almaani et al., 2017; Parikh et al., 2020).

According to the latest treatment guidelines for LN from Chinese Medical Association (2019) (CMA) (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019), LN is classified into class I (minimal mesangial LN) to class VI (advanced sclerosing LN). The currently recommended first-line treatments include the basic treatment, hydroxychloroquine (HCQ) and glucocorticoids (GC), plus immunosuppressive (IS) therapy which mainly consists of cyclophosphamide (CYC), azathioprine (AZA) and mycophenolate mofetil (MMF). The American College of Rheumatology (2012) (ACR), the European League Against Rheumatism (2019) (EULAR) and GLADEL–PANLAR Latin American (2018) provided similar recommendations (Hahn et al., 2012; Pons-Estel et al., 2018; Fanouriakis et al., 2019). In general, patients diagnosed with class III (focal LN with less than 50% of glomeruli), class IV (diffuse LN with over 50% glomeruli) and class V LN (subepithelial immune deposits and membranous LN) in combination with class III or IV require more aggressive therapy, i.e. using IS drugs in additional to the basic treatment. Besides, class III and class IV patients account for 39–72% of all six pathologic types (Wang et al., 2018). Therefore, we focused on class III and IV LN patients, including class III/IV + V (hereafter referred as 'severe LN patients').

A two-phase paradigm was recommended for severe LN patients. In the first phase, patients received induction therapy to control the acute inflammatory injury of the kidney and to achieve complete remission (defined as urine protein-to-creatinine ratio <0.5 mg/ mmol with normal kidney function). The second phase is maintenance therapy, targeting at keeping complete remission and avoiding recurrence. It is common that LN patients received lifelong treatment which led to profound economic burden. In the United States (US), the annual medical expenditures of LN exceeded $46,000 (USD) per patient (Carls et al., 2009). Another report estimated that the total annual costs including outpatient, hospitalization, non-medical costs and indirect costs of SLE was over $6,000 (USD) in Shanghai, China (Zhang et al., 2017).

CYC and MMF are listed as the first-line drugs in induction therapy, and AZA and MMF are recommended in the maintenance phase. Although CYC was not recommended for the maintenance therapy by the guidelines, it is still used in China due its relatively low cost (Zhang et al., 2014).

To our knowledge, no integrated cost-effectiveness analysis has been carried out considering the two phases of induction and maintenance and their interplay. We designed this study with structured model and surveillance of ESRD and death to assess the cost-effectiveness of current LN treatment strategies in China.

MATERIALS AND METHODS

Target Population and Therapeutic Strategies

Patients primarily diagnosed with class III, IV LN alone, and in combination with class V were targeted in our study. Milder class I and class II (mesangial proliferative LN) patients require basic treatment of HCQ and GC only without IS therapy. More severe class V (membranous LN) patients were treated based on their patient conditions and class VI (advanced sclerosing LN) patients require renal replacement therapy instead of using IS drugs. These patients were not considered in our study.

We referred to the CMA treatment guidelines for severe LN patients and current clinical practice in China in our study (Hahn et al., 2012; Pons-Estel et al., 2018; Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019; Fanouriakis et al., 2019). We considered intravenous CYC which is the main route of administration for treating LN patients in China (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019). The recommended dosage is 0.5–1 g per month for CYC and 1.5–3 g/ day for MMF as the first-line IS drugs to treat LN during the 6-months induction therapy. Besides, patients treated with CYC or MMF also received HCQ (0.3–0.5 g/ day) and pulse GC (0.5–1 g/ day) for 3 days, followed by prednisone (0.5–1 mg/ kg/ day), reducing the dose gradually each month until 0.15 mg/ kg/ day. In the maintenance therapy, AZA and MMF were recommended as the first-line IS drugs with dosage 75–100 mg/ day and less than 2 g/ day respectively. The dosage of CYC in maintenance was 0.5–1.0 g/ m^2 every 3 months (Contreras et al., 2004).

We assumed that the standard treatment (HCQ and GC) was used during the entire treatment. CYC or MMF was used for 6 months in initial induction therapy. If complete remission is achieved, patients will switch to maintenance therapy with CYC, AZA or MMF (Fanouriakis et al., 2019). Patients experiencing renal relapse after complete remission during the maintenance therapy were assumed to switch back to the same initial regimen as in the induction therapy. However, if complete remission is not achieved or only partial remission (defined as ≥50% reduction in proteinuria to subnephrotic levels) is achieved by one of the IS drugs (CYC or MMF) after 6 months, the same induction therapy is then extended for another 6 months. However, a switch to the other IS drug will be implemented if one-year induction fails under the same therapy (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019). According to ACR treatment guideline, rituximab (RTX) was typically used

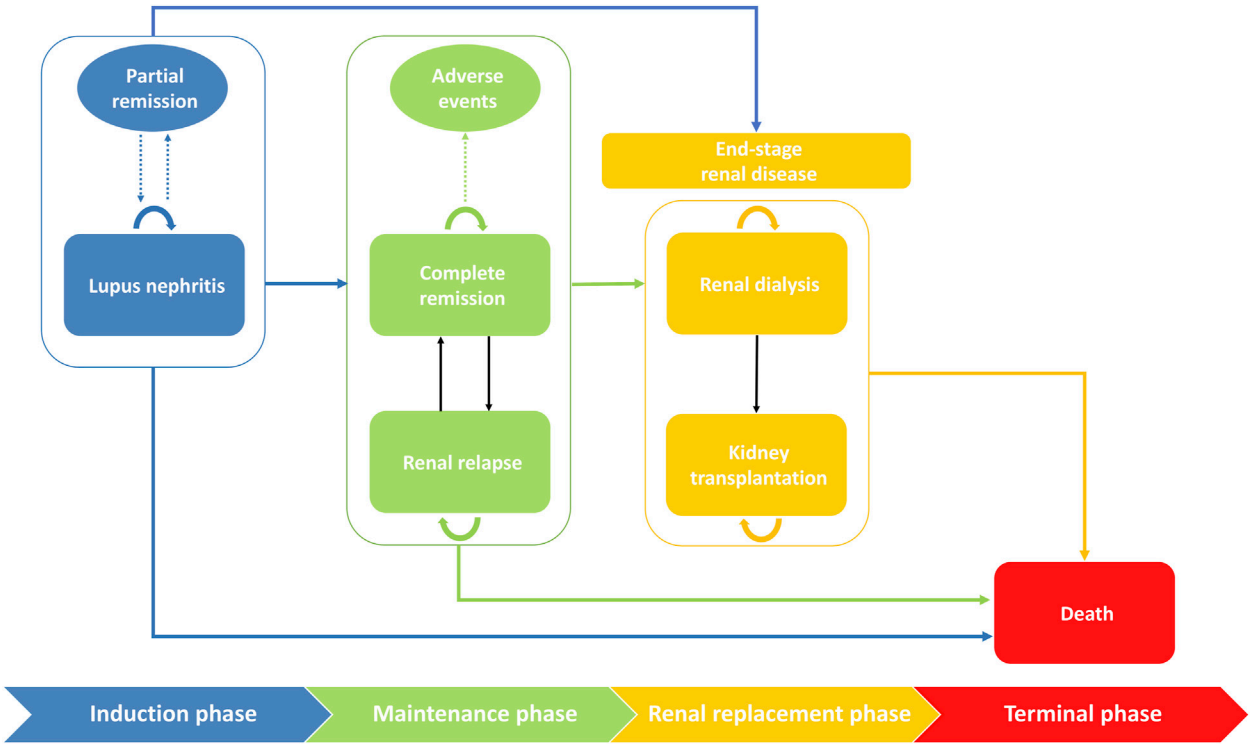

FIGURE 1 | Markov structural model of health states with disease progression with 6-months cycles. The rounded rectangles represent health states and the ovals represent the potential outcomes in each phase. Transitions between phases or between states were indicated by solid arrows. The dotted arrows indicated potential outcomes. The initial phase is induction phase where patients start to receive therapy. After achieving complete remission, patients will progress to the maintenance therapy. Patients in both induction and maintenance phase may transit to renal replacement phase. All health states have a risk of death.

when both CYC and MMF fail, and we assumed that patients could not achieve complete remission if RTX also fail (Hahn et al., 2012).

Severe LN patients should always be treated with IS drugs in additional to standard treatment (Hahn et al., 2012). CYC has long been considered the gold standard in treating LN, with superior complete remission rate and cheapest direct treatment cost, hence it is still widely used in China to achieve renal remission and prevent renal flares, although it is associated with adverse events (AEs) including bone marrow suppression, infertility and malignancy. Hence, we defined baseline strategy (S1) as: initial induction with CYC followed by CYC maintenance (CYC→CYC). We considered other strategies which comprised of combinations between two drug choices (CYC and MMF) in the initial induction and three drug choices (CYC, AZA and MMF) in the maintenance phase (S2-S6) for comparison, namely MMF→CYC, CYC→AZA, MMF→AZA, CYC→MMF and MMF→MMF.

The Analytic Model

Model Overview

A Markov model was designed to assess the cost-effectiveness of six therapeutic strategies for LN. The mean age of patients diagnosed with LN was around 30 years (Nossent and Koldingsnes, 2000; Dooley et al., 2011; Moroni et al., 2014; Wang et al., 2018), accordingly we simulated patients who met the treatment standards of severe LN from the same age. A lifetime horizon was modeled, given that continuous immunosuppressive therapy is needed to reduce SLE activity and ESRD and improve the quality of life for severe LN patients (Maroz and Segal, 2013). The life expectancy of Chinese LN patients was around 60 years, hence the lifetime horizon was set to be 30 years (Mok et al., 2013). The specific timeline of treatment has not been clearly stipulated by guidelines but it is recommended to receive at least 3-years maintenance. Therefore, we also evaluated cost-effectiveness over 3 years to assess the short-term outcomes. We adopted a societal perspective in the study and considered both direct and indirect costs. The transition period or cycle of the model was 6-months covering the induction period and evaluation of the therapy (Dooley et al., 2011). Hence in the model, we ran a total of 60 cycles to simulate the lifetime effect of disease progression with different treatment strategies. Main outcomes from the model included the cost of each patient, cumulative quality-adjusted life years (QALYs), incremental cost per QALY and incremental cost-effectiveness ratio (ICER). ICER indicated additional costs per QALY gained compared with the previous least costly strategy. We also simulated the disease trends of ESRD and death.

Model Structure

We considered four main phases of patient management, namely induction, maintenance, renal replacement, and terminal phase,

TABLE 1 | Transition probabilities related to disease progress and different treatments[a].

6-months transition	Estimate (%)	Range for sensitivity analysis[b] (%)	References
Induction therapy with immunosuppressive drugs, from lupus nephritis			
To complete remission with CYC	40.84	21.74–66.67	Moroni et al. (2014)
To complete remission with MMF	31.37	25.00–54.00	Moroni et al. (2014)
To complete remission with RTX	45.78	14.20–72.70	Moroni et al. (2014)
To ESRD	0.80	0.71–0.84	Croca et al. (2011)
To lupus-related death	0.80	0.48–1.87	Croca et al. (2011)
To ESRD, when treatment failure[c]	2.48	0.81–8.00	Korbet et al. (2000)
To lupus-related death, when treatment failure	2.83	2.14–3.64	Korbet et al. (2000)
Maintenance therapy with immunosuppressive drugs, from complete remission			
To renal relapse with CYC	5.00	3.30–7.73	Nee et al. (2015); Pons-Estel et al. (2018)
To ESRD with CYC	0.45	0.23–0.96	Zhang et al. (2014)
To lupus-related death with CYC	1.84	0.33–13.08	Nee et al. (2015); Tunnicliffe et al. (2018)
To renal relapse with AZA	3.64	2.34–5.87	Nee et al. (2015)
To ESRD with AZA	0.30	0.06–1.60	Nee et al. (2015)
To lupus-related death with AZA	0.25	0.04–1.57	Nee et al. (2015)
To renal relapse with MMF	1.85	1.22–2.86	Nee et al. (2015)
To ESRD with MMF	0.12	0.02–0.63	Nee et al. (2015)
To lupus-related death with MMF	0.43	0.07–2.85	Nee et al. (2015)
Renal replacement therapy			
Transition probability to KT after receiving renal dialysis	0.85	0.36–2.01	Yikui et al. (2015); Wang et al. (2019)
Transition probability to death after receiving renal dialysis	4.29	1.00–7.47	Wu et al. (2014); Tsai et al. (2019)
Transition probability to death after receiving KT	0.29	0.19–0.37	Wu et al. (2014); Tsai et al. (2019)

AZA, azathioprine; CYC, cyclophosphamide; ESRD, end-stage renal disease; KT, kidney transplantation; MMF, mycophenolate mofetil; RTX, rituximab.
[a]The estimates and validations regarding the treatment with immunosuppressive drugs were referenced to Bernardo et al., 2018 (Pons-Estel et al., 2018) and (Tunnicliffe et al., 2018).
[b]Ranges for the uncertainty analysis were either obtained from the range of estimates in systematic reviews, or from the 95% confidence intervals from a specific study.
[c]No complete remission after treatment with immunosuppressive drugs.

with six health status including LN, complete remission, renal relapse, renal dialysis, kidney transplantation and death in our model (**Figure 1**). All severe LN patients received the induction therapy. Patients who achieved complete remission would progress to the maintenance phase but may still have a risk of relapse. A systematic review and meta-analysis found that renal dialysis was always considered as the initial renal replacement therapy, prior to transplantation (Swai et al., 2020). For simplicity, we assumed in our model that patients with ESRD received dialysis first, and may further require kidney transplantation if the patient's condition deteriorated (Adler et al., 2006).

Model Input

Transition Probability

We extracted the relevant transition probabilities between health status and their ranges for uncertainty analysis, based on an extensive literature review of primary studies and meta-analyses (**Table 1**). We extracted the drug efficiency data in induction phase, prioritizing head-to-head comparison studies. These parameters were converted for use in our model with a 6-months cycle (detailed description in the Supporting Material).

According to the guideline in from CMA, after the induction therapy, standard evaluation methods including clinical symptoms (kidney function) and indicators (urine protein-to-creatinine ratio) are used to measure the health status. Those who enter the maintenance therapy after reaching complete remission must have matched the above assessment (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019). In the simulation, we assumed that the effect of maintenance therapy was independent of previous states during induction (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019).

We searched PubMed, Web of Science, Google Scholar, China National Knowledge Infrastructure and Embase for articles with the keywords "lupus nephritis", "induction", "cyclophosphamide", "mycophenolate mofetil" or/and "rituximab" in induction therapy. A similar search was carried out by changing the keyword "induction" to "maintenance", and added "azathioprine" in maintenance therapy. In renal replacement phase, we used the keywords "end-stage renal disease", "kidney transplantation", "death" or/and "mortality" without restriction on language between 1980 and 2020. To obtain head-to-head transition probability, we reviewed the literature extensively. For instance, in induction therapy, transitions from LN to complete remission including CYC, MMF and RTX therapy were based on a clinical observational study, with converting the annual transition probability to 6-months cycle (Moroni et al., 2014).

Quality-Adjusted Life Years and Costs

We used QALYs as the utility measurement, calculated by multiplying the utility score by time spent in a state (Whitehead and Ali, 2010). The utility scores of various health status measured by EQ-5D index were extracted from the

literature (Liem et al., 2008; Mohara et al., 2014). The state of death was assigned a utility score of 0, and the other states were assigned health utility score ranging from 0.56 to 0.94 (**Supplementary Table S1**). Due to the higher treatment costs for AEs and the significant infertility risk due to CYC, the estimated utility score for complete remission and renal relapse after being treated with CYC was lower than that treated with other IS drugs (McDermott and Powell, 1996; Nee et al., 2015; Jones et al., 2019).

In the model, we considered total costs associated with treatment and management of LN, including direct costs and indirect costs. Direct costs consisted of direct health care costs (drugs, treatment-related AEs, medical devices, diagnostic tests, laboratory tests, hospital admission fee, etc.) and direct non-medical costs (transportation, accommodation expenses and social service such as retraining). AEs included major and minor infections, pneumonia, gastrointestinal manifestation, and leucopenia induced by IS drugs, and diabetes, hypertension, fractures, and eye diseases induced by GC and HCQ. Risks of these AEs and the related costs were presented in (**Supplementary Tables S2–4**). Prices of GC and HCQ and IS drugs were obtained from Hospital Information System, the Third Affiliated Hospital of Sun Yat-sen University, a major medical center in China and the evaluation of the costs of AE was also based on the system by two physicians (XZ and ZL) (The Third Affiliated Hospital of Sun Yat-sen University, 2019). Indirect costs included productivity loss, calculated by multiplying gross value of daily average income per capita in China by days off work (**Supplementary Table S5**); (Jo, 2014). The major cost for living donor kidney transplantation was accrued shortly after the treatment, and the direct and indirect health costs dropped quickly afterwards (**Supplementary Table 1**).

Considering the similar utilities between hemodialysis (HD) and peritoneal dialysis (PD) and the more popular use of HD in China (Wang et al., 2006; Liem et al., 2008; Zhang and Zuo, 2016). we considered the costs of HD for patients with ESRD in the analysis. The costs of dialysis in renal replacement phase included medication, consultation, laboratory and radiological investigation, dialysis solution, machine depreciation and other costs. Similarly, we considered the costs of living donor kidney transplantation in the study which is most common in China. Costs of kidney transplantation also included surgical and nursing, laboratory and testing, immunosuppressive agents, accommodation and other costs (Xiaoming et al., 2012). All costs were converted to 2019 prices using the consumer price indices from 2003 to 2019, and from Chinese Yuan (CNY, ¥) to U.S. dollars (USD, $) using the exchange rate in 2019 (1 USD = 6.87 CNY) (National Bureau of Statistics of China, 2019). QALY and costs were discounted at a rate of 1.5% per 6-months cycle (3% per year) (Chhatwal et al., 2016). One times gross domestic product (GDP) per capita (¥70,892 or US$10,319, 2019) in mainland China was considered as the willingness-to-pay (WTP) threshold, which was considered highly cost–effective, and three times GDP per capita was also adopted as the threshold for being cost-effective (¥212,676 or US$30,957, 2019) (Marseille et al., 2015; National Bureau of Statistics of China, 2019).

Uncertainty Analysis

We assessed the uncertainty of the estimates with deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) over the lifetime horizon. Key parameters including the transition probability between health states, costs and utility of each health state and discount rate were varied sequentially in DSA (**Table 1**; **Supplementary Table S1**). Ranges for the uncertainty analysis were either obtained from the range of estimates in systematic reviews, or from the 95% confidence intervals from a specific study. The outcome was presented in tornado plots, showing the most influential parameters on model results. In PSA, pre-defined parameters were re-sampled from respective distributions with 1,000 simulated cohorts. Dirichlet, binomial, normal and gamma distributions were assumed in the transition probabilities between states, discount rate, utility and costs respectively (Chen et al., 2016).

RESULTS

Table 2 summarized cost effectiveness and outcomes of different LN treatment strategies by 3-years and lifetime horizon. The efficiency frontiers at lifetime horizons are presented in **Supplementary Figure S1**. For a 3-years horizon, treating LN patients with CYC induction therapy and AZA maintenance therapy (S3, $448 per QALY gained) was most cost-effective compared with the baseline strategy (S1: CYC→CYC), with 0.218 more QALYs (**Table 2**). S4 (MMF→AZA) was the next cost-effective strategy if one is willing to pay $22,262 more than S3 (CYC→AZA) at a WTP of three times GDP per capita (US$30,957) but was then dominated by the most effective strategy S6 (MMF→MMF) after 24 years (**Supplementary Figure S2**). The proportions of patients experiencing renal replacement was lower for strategies with MMF maintenance (S5 and S6), and there were lower complete remission rate and higher all-cause mortality for strategies with CYC maintenance (S1 and S2, **Table 2**). For a lifetime horizon, CYC induction and AZA maintenance therapy (S3) was also the most cost-effective strategy which was associated with 48.9, 5.8 and 40.8% complete remission rate, risk of renal replacement and all-cause mortality respectively. However, S6 (MMF→MMF) achieved the highest complete remission rate and the lowest risk of renal replacement and all-cause mortality, at 57.2, 3.3 and 36.0% respectively among all cost-effective strategies. Again, strategies with CYC maintenance (S1 and S2) had noticeably lower complete remission rate and higher mortality. Due to the small number of cases who developed ESRD (**Supplementary Figure S3**, costs were mainly driven drug costs (CYC, MMF or AZA). Cost associated with ESRD increased disproportionately in the long run but still much lower than the drug costs.

Sensitivity Analysis

We conducted DSA for the most cost-effective strategy S3 (CYC→AZA) for a lifetime horizon (**Figure 2**). The most influential parameter that affected ICER was the risk of ESRD after complete remission during AZA maintenance therapy. Other influential parameters included the mortality risk

TABLE 2 | Base-case cost-effectiveness outcomes of different strategies for LN treatment, and predicted cumulative incidence of complete remission, renal replacement and all-cause mortality.

Strategy	Cumulative costs (US$)	Cumulative QALYs	Incremental costs (US$)	Incremental QALYs	ICER (US$/QALY)	Complete remission[a] (%)	Renal replacement[b] (%)	All-cause mortality[c] (%)
3-years horizon								
S1: CYC→CYC	15,874	2.156	–	–	–	75.9	2.9	7.9
S3: CYC→AZA	15,972	2.374	98	0.218	448	82.5	2.5	3.4
S2: MMF→CYC	17,469	2.308	1,595	0.152	Dominated	75.4	3.0	7.6
S4: MMF→AZA	17,484	2.442	1,512	0.068	22,262	81.8	2.6	3.5
S5: CYC→MMF	17,594	2.384	1,622	0.010	Dominated	85.9	2.0	3.2
S6: MMF→MMF	18,897	2.452	1,413	0.010	136,075	85.3	2.1	3.4
Lifetime horizon								
S1: CYC→CYC	70,286	9.745	–	–	–	18.7	5.1	73.7
S2: MMF→CYC	76,480	10.702	6,194	0.957	Dominated	18.3	5.2	73.2
S3: CYC→AZA	82,540	14.287	12,254	4.542	2,698	48.9	5.8	40.8
S4: MMF→AZA	88,393	14.866	5,853	0.579	Dominated	47.1	6.0	41.4
S5: CYC→MMF	90,031	14.869	7,491	0.582	Dominated	58.5	3.2	35.5
S6: MMF→MMF	93,708	15.517	11,168	1.230	9,079	57.2	3.3	36.0

AZA, azathioprine; CYC, cyclophosphamide; ICER, incremental cost-effectiveness ratios; MMF, mycophenolate mofetil; QALYs, quality-adjusted life years.

[a]*Chi-squared test for equality of proportions:* p < *0.001 among strategies at 3-years horizon and* p < *0.001 among strategies at lifetime horizon.*

[b]*Renal replacement included renal dialysis and kidney transplantation. Chi-squared test for equality of proportions:* p = *0.658 among strategies at 3-years horizon and* p = *0.005 among strategies at lifetime horizon.*

[c]*Chi-squared test:* p < *0.001 among strategies at 3-years horizon and* p < *0.001 among strategies at lifetime horizon.*

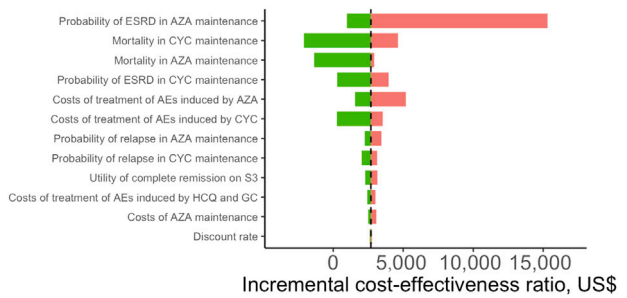

FIGURE 2 | Tornado plot of deterministic sensitivity analysis for patients with lupus nephritis receiving the most cost-effective strategy (S3: CYC→AZA) compared with the baseline strategy (S1: CYC→CYC) over a lifetime horizon. The base-case result is presented by vertical dashed line. The length of the bars reflects the degree of parameters that influence quality-adjusted life years. Only the top 12 most influential parameters were presented. HCQ, hydroxychloroquine; GC, glucocorticoids; CYC, cyclophosphamide; AZA, azathioprine; ESRD, end-stage renal disease; AEs, adverse events.

associated with CYC and AZA maintenance therapy, probability of ESRD in CYC maintenance therapy, and costs of treatment-related AEs by AZA and CYC. In PSA we estimated that at the WTP of one times GDP per capita, most simulated cohorts treated with S6 (MMF in both treatment phases) over a lifetime horizon were under the ceiling ratio, and more than 99% of the cohorts were under the ceiling ratio for the three times GDP per capita WTP, meaning the cost-effectiveness. S6 had the highest acceptability of 34% among all strategies, followed by S4 (MMF→AZA) being cost-effective with 28% probability (**Figure 3**). The cost-effectiveness acceptability of S4 (MMF→AZA) and S5 (CYC→MMF) became stable whereas the probability of being cost-effective for S6 increased to 40% at the three times GDP per capita WTP threshold.

DISCUSSION

LN with subsequent development of ESRD has led to substantial mortality burden among patients with SLE (Almaani et al., 2017). Current LN therapies may cause complications such as infections, pneumonia, toxic retinopathy and diabetes which require further treatment and are associated with high financial burden. While various LN treatment options have been recommended, our study is first to evaluate the cost-effectiveness of these treatment strategies in an integrated framework considering induction, maintenance, renal replacement and terminal phases in China.

We found that the strategy of CYC induction followed by AZA maintenance therapy (S3) was the most cost-effective for both the 3-years and lifetime horizon. A study in Thailand found that the same strategy was the only cost-saving strategy (Mohara et al., 2014). The most effective strategy S6 (MMF → MMF) was not

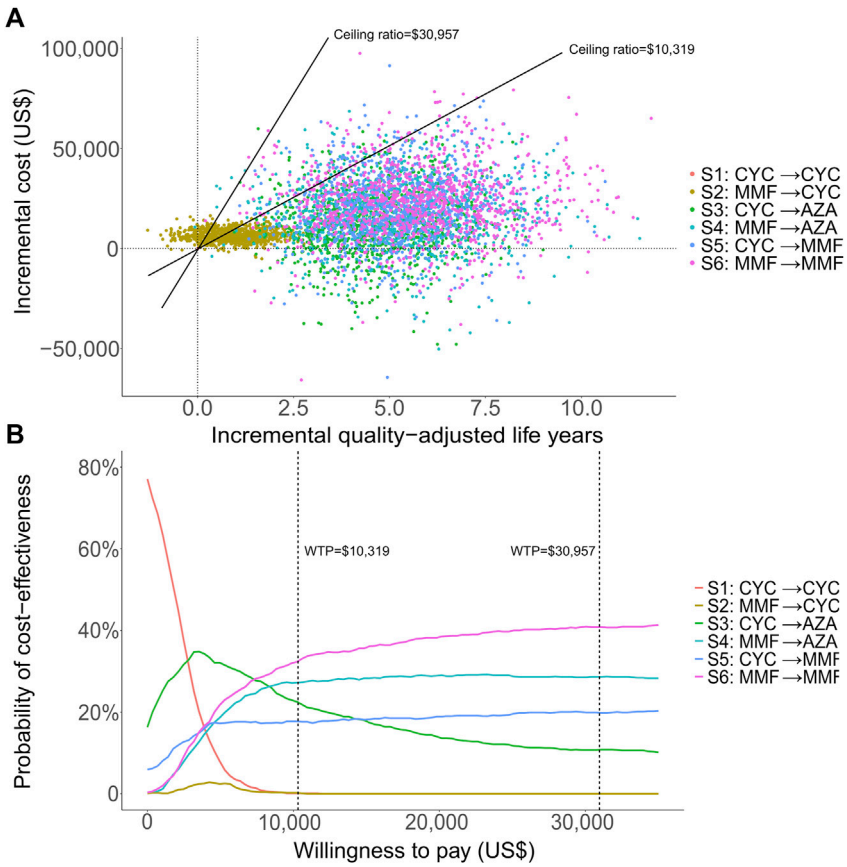

FIGURE 3 | Probabilistic analytic results for the scenario over a lifetime horizon: the incremental cost-effectiveness differences simulated with 1,000 patients **(A)** and the cost-effectiveness acceptability curves of all strategies **(B)**. One-time and three-time gross domestic product per capita were used for the willingness to pay thresholds, at US$10,319 and US$30,957 respectively.

cost-effective at both WTP thresholds for a 3-years time horizon. However, it became affordable and most cost-effective for a lifetime horizon probably due to a lower relapse rate and risk of developing ESRD for MMF maintenance compared to AZA, which compensated the relatively high drug cost for MMF (Dooley et al., 2011). The cost-effective treatment identified in our study is likely applicable in the Asian settings. Although no similar cost-effectiveness study has been conducted in high income countries considering the induction and maintenance therapy together, several studies examined cost-effectiveness of the induction therapy and maintenance therapy separately. In the United Kingdom, MMF is costing US$3,100 less than CYC over the 24-week period in induction therapy based on the price in 2005 (Wilson et al., 2007). In the United States, MMF was found to be more cost-effective, with an ICER of $6,454/QALY compared to AZA in lifetime maintenance therapy (Nee et al., 2015). These studies showed that MMF was cost-effective for both induction and maintenance therapy, consistent with our results. Our study results are likely applicable to high and middle income countries.

Compared with other strategies, MMF maintenance was associated with the lowest risks of ESRD and death over 30 years (**Table 2**; **Supplementary Figure S3**). S5 (CYC→MMF) was also dominated by S6 (MMF→MMF) in our study. Further, S3 (CYC→AZA) and S4 (MMF→AZA) resulted in higher risk of ESRD than S6 (MMF→MMF) when longer course of treatment was adopted, with the discrepancy becoming more prominent starting from 5 years of treatment (**Supplementary Figure S3**). This was partly due to the higher renal relapse rate in AZA maintenance, which was also demonstrated by a previous systematic review (Tunnicliffe et al., 2018). We also showed that use of CYC in long-term maintenance therapy would result in lower complete remission rate, and higher risk of ESRD and death. A meta-analysis also found that using MMF was likely to produce better clinical outcome than CYC (Liu et al., 2012). In China, AZA treatment is subsidized, and the use of CYC maintenance for treating sever LN patients should be discouraged.

Disease progression rate to ESRD during AZA maintenance was found to be the most influential factor affecting the cost-effectiveness of S3 (CYC→AZA) (**Figure 2**). Clinically, identifying patients with higher risk of developing ESRD is important to reduce the risk of morbidity and mortality, which was also an important factor affecting cost-effectiveness. In the US, the incidence of LN-associated ESRD increased 5 times approximately from 1982 to 2004 (Maroz and Segal, 2013). A need for careful monitoring of severe LN patients for progression to ESRD is recommended, including continuous immunosuppressive medication, regular follow-up, histopathologic

examination, assessment of renal indices and treatment response of LN during maintenance (Hahn et al., 2012).

As a validation of our model, considering the most cost-effective strategy (S3: CYC → AZA) and most effective strategy (S6: MMF → MMF), the risk of developing ESRD were 4.0 and 2.8% respectively by 6 years, consistent with a meta-analysis analyzing studies with follow-up from 3 to 6 years, in which the pooled risk of developing ESRD were 30 and 17 per 1,000 during maintenance therapy using AZA and MMF respectively (Tunnicliffe et al., 2018). The estimated risks of 10-years all-cause death were 11.8 and 10.7% under treatment with S3 (CYC → AZA) and S6 (MMF → MMF), similar to another epidemiological study showing that the patient survival in Asia (Hong Kong, Iran, and Japan) reached 92% with the effect of immunosuppressive therapies over the same time span (Yap and Chan, 2015).

Our study has several limitations. First, some parameters were not available from China. We used available data from other countries which were most relevant. Heath-related quality of life in LN patients was estimated from several other countries. Second, the dosage of CYC in maintenance therapy was not obtained from official guidelines as it is no longer recommended as first-line therapy (Hahn et al., 2012; Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019). We assumed the decrease to half of the dosage in the maintenance phase was reflected in the drug price. Sensitivity analysis also showed that the cost of CYC had limited impact on the results. Third, some losses were difficult to measure in terms of exact costs, such as ovarian failure due to CYC where there is no effective way of prevention and treatment (McDermott and Powell, 1996). We also did not consider withdrawal of therapy due to more severe but rare AEs or other reasons. For example, monitoring of peripheral T lymphocytes are recommended when patients receive immunosuppression therapy (Houssiau et al., 2010). Dose reduction or even withdrawal of MMF should be considered if lymphocytes continue to decline, or CD4 + T cells are less than 200/ μL (Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group, 2019). Lastly, though we have restricted our analysis to class III, IV, and III/IV + V LN patients and considered combination of drug options at the induction and maintenance therapy in each of which patients were more homogeneous in terms of disease severity, we could not rule out residual confounding by indication. It is also uncertain whether IS drug failure in the induction therapy would modify the efficacy of another IS drugs in the following induction or maintenance therapy, and we assumed efficacy of each therapy was independent.

In conclusion, our study demonstrated that for both a 3-years and lifetime horizon, the most cost-effective strategy for treating severe LN patients in China was CYC induction therapy, followed by AZA maintenance therapy at the three times GDP per capita WTP threshold. The strategy of using MMF in both induction and maintenance became cost-effective under the one times GDP per capita WTP threshold for a lifetime horizon, with clinical benefits of achieving the lowest ESRD and mortality among strategies considered. Monitoring of patients during maintenance for progression to ESRD is recommended.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

ZD: Study design, data acquisition, data analysis and manuscript drafting; XZ: Data acquisition, data analysis and data interpretation; IW: Data interpretation and manuscript revision; EL: Study design, data interpretation, manuscript drafting, revision and approval; ZL: Study design, manuscript revision and approval. All authors critical approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.678301/full#supplementary-material

REFERENCES

Adler, M., Chambers, S., Edwards, C., Neild, G., and Isenberg, D. (2006). An Assessment of Renal Failure in an SLE Cohort with Special Reference to Ethnicity, over a 25-year Period. *Rheumatology (Oxford)* 45 (9), 1144–1147. doi:10.1093/rheumatology/kel039

Almaani, S., Meara, A., and Rovin, B. H. (2017). Update on Lupus Nephritis. *Clin. J. Am. Soc. Nephrol.* 12 (5), 825–835. doi:10.2215/CJN.05780616

Carls, G., Li, T., Panopalis, P., Wang, S., Mell, A. G., Gibson, T. B., et al. (2009). Direct and Indirect Costs to Employers of Patients with Systemic Lupus Erythematosus with and without Nephritis. *J. Occup. Environ. Med.* 51 (1), 66–79. doi:10.1097/JOM.0b013e31818a405a

Chen, Q., Ayer, T., and Chhatwal, J. (2016). Sensitivity Analysis in Sequential Decision Models. *Med. Decis. Making* 37 (2), 243–252. doi:10.1177/0272989X16670605

Chhatwal, J., Jayasuriya, S., and Elbasha, E. H. (2016). Changing Cycle Lengths in State-Transition Models: Challenges and Solutions. *Med. Decis. Making* 36 (8), 952–964. doi:10.1177/0272989X16656165

Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis Writing Group (2019). Chinese Guidelines for Diagnostic and Treatment of Lupus Nephritis. *Natl. Med. J. China*.

Contreras, G., Pardo, V., Leclercq, B., Lenz, O., Tozman, E., O'Nan, P., et al. (2004). Sequential Therapies for Proliferative Lupus Nephritis. *N. Engl. J. Med.* 350 (10), 971–980. doi:10.1056/NEJMoa031855

Croca, S. C., Rodrigues, T., and Isenberg, D. A. (2011). Assessment of a Lupus Nephritis Cohort over a 30-year Period. *Rheumatology (Oxford)* 50 (8), 1424–1430. doi:10.1093/rheumatology/ker101

Dooley, M. A., Jayne, D., Ginzler, E. M., Isenberg, D., Olsen, N. J., Wofsy, D., et al. (2011). Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis. *N. Engl. J. Med.* 365 (20), 1886–1895. doi:10.1056/NEJMoa1014460

Fanouriakis, A., Kostopoulou, M., Alunno, A., Aringer, M., Bajema, I., Boletis, J. N., et al. (2019). 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus. *Ann. Rheum. Dis.* 78 (6), 736–745. doi:10.1136/annrheumdis-2019-215089

Hahn, B. H., McMahon, M. A., Wilkinson, A., Wallace, W. D., Daikh, D. I., Fitzgerald, J. D., et al. (2012). American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis. *Arthritis Care Res.* 64, 797–808. doi:10.1002/acr.21664

Houssiau, F. A., D'Cruz, D., Sangle, S., Remy, P., Vasconcelos, C., Petrovic, R., et al. (2010). Azathioprine versus Mycophenolate Mofetil for Long-Term Immunosuppression in Lupus Nephritis: Results from the MAINTAIN Nephritis Trial. *Ann. Rheum. Dis.* 69 (12), 2083–2089. doi:10.1136/ard.2010.131995

Jo, C. (2014). Cost-of-illness Studies: Concepts, Scopes, and Methods. *Clin. Mol. Hepatol.* 20 (4), 327–337. doi:10.3350/cmh.2014.20.4.327

Jones, R. B., Hiemstra, T. F., Ballarin, J., Blockmans, D. E., Brogan, P., Bruchfeld, A., et al. (2019). Mycophenolate Mofetil versus Cyclophosphamide for Remission Induction in ANCA-Associated Vasculitis: a Randomised, Non-inferiority Trial. *Ann. Rheum. Dis.* 78 (3), 399–405. doi:10.1136/annrheumdis-2018-214245

Korbet, S. M., Lewis, E. J., Schwartz, M. M., Reichlin, M., Evans, J., and Rohde, R. D. (2000). Factors Predictive of Outcome in Severe Lupus Nephritis. Lupus Nephritis Collaborative Study Group. *Am. J. Kidney Dis.* 35 (5), 904–914. doi:10.1016/s0272-6386(00)70262-9

Liem, Y. S., Bosch, J. L., and Hunink, M. G. (2008). Preference-based Quality of Life of Patients on Renal Replacement Therapy: a Systematic Review and Meta-Analysis. *Value Health* 11 (4), 733–741. doi:10.1111/j.1524-4733.2007.00308.x

Liu, L. L., Jiang, Y., Wang, L. N., Yao, L., and Li, Z. L. (2012). Efficacy and Safety of Mycophenolate Mofetil versus Cyclophosphamide for Induction Therapy of Lupus Nephritis: a Meta-Analysis of Randomized Controlled Trials. *Drugs* 72 (11), 1521–1533. doi:10.2165/11635030-000000000-00000

Maroz, N., and Segal, M. S. (2013). Lupus Nephritis and End-Stage Kidney Disease. *Am. J. Med. Sci.* 346 (4), 319–323. doi:10.1097/MAJ.0b013e31827f4ee3

Marseille, E., Larson, B., Kazi, D. S., Kahn, J. G., and Rosen, S. (2015). Thresholds for the Cost-Effectiveness of Interventions: Alternative Approaches. *Bull. World Health Organ.* 93 (2), 118–124. doi:10.2471/BLT.14.138206

McDermott, E. M., and Powell, R. J. (1996). Incidence of Ovarian Failure in Systemic Lupus Erythematosus after Treatment with Pulse Cyclophosphamide. *Ann. Rheum. Dis.* 55 (4), 224–229. doi:10.1136/ard.55.4.224

Mohara, A., Pérez Velasco, R., Praditsitthikorn, N., Avihingsanon, Y., and Teerawattananon, Y. (2014). A Cost-Utility Analysis of Alternative Drug Regimens for Newly Diagnosed Severe Lupus Nephritis Patients in Thailand. *Rheumatology (Oxford)* 53 (1), 138–144. doi:10.1093/rheumatology/ket304

Mok, C. C., Kwok, R. C., and Yip, P. S. (2013). Effect of Renal Disease on the Standardized Mortality Ratio and Life Expectancy of Patients with Systemic Lupus Erythematosus. *Arthritis Rheum.* 65 (8), 2154–2160. doi:10.1002/art.38006

Moroni, G., Raffiotta, F., Trezzi, B., Giglio, E., Mezzina, N., Del Papa, N., et al. (2014). Rituximab vs Mycophenolate and vs Cyclophosphamide Pulses for Induction Therapy of Active Lupus Nephritis: a Clinical Observational Study. *Rheumatology (Oxford)* 53 (9), 1570–1577. doi:10.1093/rheumatology/ket462

National Bureau of Statistics of China (2019). Annual Data. Available at: http://data.stats.gov.cn/.

Nee, R., Rivera, I., Little, D. J., Yuan, C. M., and Abbott, K. C. (2015). Cost-utility Analysis of Mycophenolate Mofetil versus Azathioprine Based Regimens for Maintenance Therapy of Proliferative Lupus Nephritis. *Int. J. Nephrol.* 2015, 917567–917613. doi:10.1155/2015/917567

Nossent, H. C., and Koldingsnes, W. (2000). Long-term Efficacy of Azathioprine Treatment for Proliferative Lupus Nephritis. *Rheumatology (Oxford)* 39, 969–974. doi:10.1093/rheumatology/39.9.969

Parikh, S. V., Almaani, S., Brodsky, S., and Rovin, B. H. (2020). Update on Lupus Nephritis: Core Curriculum 2020. *Am. J. Kidney Dis.* 76 (2), 265–281. doi:10.1053/j.ajkd.2019.10.017

Pons-Estel, B. A., Bonfa, E., Soriano, E. R., Cardiel, M. H., Izcovich, A., Popoff, F., et al. (2018). First Latin American clinical practice guidelines for the treatment of systemic lupus erythematosus: Latin American Group for the Study of Lupus (GLADEL, Grupo Latino Americano de Estudio del Lupus)-Pan-American League of Associations of Rheumatology (PANLAR). *Ann. Rheum. Dis.* 77 (11), 1549–1557. doi:10.1136/annrheumdis-2018-213512

Swai, J., Zhao, X., Noube, J. R., and Ming, G. (2020). Systematic Review and Meta-Analysis of Clinical Outcomes Comparison between Different Initial Dialysis Modalities in End-Stage Renal Disease Patients Due to Lupus Nephritis Prior to Renal Transplantation. *BMC Nephrol.* 21, 156. doi:10.1186/s12882-020-01811-y

The Third Affiliated Hospital of Sun Yat-sen University (2019). Hospital Information System. Available at: https://www.zssy.com.cn.

Tsai, W. T., Chang, H. C., Wang, C. T., Chiang, B. L., and Lin, Y. T. (2019). Long-term Outcomes in Lupus Patients Receiving Different Renal Replacement Therapy. *J. Microbiol. Immunol. Infect.* 52 (4), 648–653. doi:10.1016/j.jmii.2018.12.010

Tunnicliffe, D. J., Palmer, S. C., Henderson, L., Masson, P., Craig, J. C., Tong, A., et al. (2018). Immunosuppressive Treatment for Proliferative Lupus Nephritis. *Cochrane Database Syst. Rev.* 6 (6), CD002922. doi:10.1002/14651858.CD002922.pub4

Wang, F., Yang, C., Long, J., Zhao, X., Tang, W., Zhang, D., et al. (2019). Executive Summary for the 2015 Annual Data Report of the China Kidney Disease Network (CK-NET). *Kidney Int.* 95 (3), 501–505. doi:10.1016/j.kint.2018.11.011

Wang, H., Ren, Y. L., Chang, J., Gu, L., and Sun, L. Y. (2018). A Systematic Review and Meta-Analysis of Prevalence of Biopsy-Proven Lupus Nephritis. *Arch. Rheumatol.* 33 (1), 17–25. doi:10.5606/ArchRheumatol.2017.6127

Wang, J. J., Lu, Y. E., Shan-Lian, H. U., Hao, C. P., and Han, F. (2006). Disease burden on Dialysis Therapy. *Chin. Health Resour.*

Whitehead, S. J., and Ali, S. (2010). Health Outcomes in Economic Evaluation: the QALY and Utilities. *Br. Med. Bull.* 96 (1), 5–21. doi:10.1093/bmb/ldq033

Wilson, E. C., Jayne, D. R., Dellow, E., and Fordham, R. J. (2007). The Cost-Effectiveness of Mycophenolate Mofetil as Firstline Therapy in Active Lupus Nephritis. *Rheumatology (Oxford)* 46 (7), 1096–1101. doi:10.1093/rheumatology/kem054

Wu, M. J., Lo, Y. C., Lan, J. L., Yu, T. M., Shu, K. H., Chen, D. Y., et al. (2014). Outcome of Lupus Nephritis after Entering into End-Stage Renal Disease and Comparison between Different Treatment Modalities: A Nationwide Population-Based Cohort Study in Taiwan. *Transpl. Proc* 46 (2), 339–341. doi:10.1016/j.transproceed.2013.11.080

Xiaoming, P., Heli, X., Chenguang, D., Hua, L., Guozhen, C., and Mao, T. (2012). Cost of Two Different Therapies for End-Stage Renal Disease in Northwest China. *J. Med. Colleges PLA(China)* 27 (2), 80–86.

Yap, D. Y., and Chan, T. M. (2015). Lupus Nephritis in Asia: Clinical Features and Management. *Kidney Dis. (Basel)* 1 (2), 100–109. doi:10.1159/000430458

Yap, D. Y., Tang, C. S., Ma, M. K., Lam, M. F., and Chan, T. M. (2012). Survival Analysis and Causes of Mortality in Patients with Lupus Nephritis. *Nephrol. Dial. Transpl.* 27 (8), 3248–3254. doi:10.1093/ndt/gfs073

Yikui, S., Ping, Z., Linge, H., Xinyue, Y., and Hongxiu, L. (2015). Effect of Maintenance Hemodialysis on Prognosis and Survival of Patients with End-Stage Renal Disease. *Shanxi Med. J.*

Zhang, L., Lu, G. H., Ye, S., Wu, B., Shen, Y., and Li, T. (2017). Treatment Adherence and Disease burden of Individuals with Rheumatic Diseases Admitted as Outpatients to a Large Rheumatology center in Shanghai, China. *Patient Prefer Adherence* 11, 1591–1601. doi:10.2147/PPA.S144624

Zhang, L., and Zuo, L. (2016). Current burden of End-Stage Kidney Disease and its Future Trend in China. *Clin. Nephrol.* 86 (S1), 27–28. doi:10.5414/CNP86S104

Zhang, X. W., Li, C., Ma, X. X., Zhao, J. X., An, Y., Liu, S., et al. (2014). Short-interval Lower-Dose Intravenous Cyclophosphamide as Induction and

Maintenance Therapy for Lupus Nephritis: a Prospective Observational Study. *Clin. Rheumatol.* 33 (7), 939–945. doi:10.1007/s10067-014-2590-6

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GLOSSARY

LN Lupus nephritis
SLE Systemic lupus erythematosus
ESRD End-stage renal disease
CMA Chinese Medical Association
ACR American College of Rheumatology
EULAR European League Against Rheumatism
HCQ Hydroxychloroquine
GC Glucocorticoids
IS Immunosuppressive
US United States
USD ($) United States Dollar
CYC Cyclophosphamide
AZA Azathioprine
MMF Mycophenolate mofetil
RTX Rituximab
AE Adverse event
QALY Quality-adjusted life year
ICER Incremental cost-effectiveness ratio
HD Hemodialysis
PD Peritoneal dialysis
CNY (¥) Chinese Yuan
GDP Gross domestic product
WTP Willingness-to-pay
DSA Deterministic sensitivity analysis
PSA Probabilistic sensitivity analysis
S1 Strategy 1
S2 Strategy 2
S3 Strategy 3
S4 Strategy 4
S5 Strategy 5
S6 Strategy 6

frontiers in Pharmacology

ORIGINAL RESEARCH
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Yisaipu® Provide AS Patients With an Economical Therapeutic Option While Original Biologicals are More Advantageous in the COVID-19 Epidemic Situation

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Objectives: Anti-tumor necrosis factor (TNF) agents have been regarded as the most effective treatment for ankylosing spondylitis (AS) so far. However, economic factors limited the prescription of original biologicals in China. Yisaipu® is a biosimilar for etanercept as pre fill syringes (PFS), which has entered China's national medical insurance catalog for more than 10 yr and was widely used because it greatly reduced the economic burden of AS patients. Yisaipu® is provided subcutaneous injection in hospital setting only. We collected clinical data of AS patients before, during and after COVID-19 epidemic, in an attempt to investigate the advantages and disadvantages of original biologicals and Yisaipu® during regular follow up and COVID-19 epidemic.

Methods: AS patients who received original biologicals or Yisaipu® in our department for more than 1 yr were included in our study. General data, demographic characteristics, disease activity, quality of life and medical compliance were collected from regular visits. The patients were followed up through telephone interviews from April 20th to 27th, 2020 about the overall impact of the COVID-19 epidemic.

Results: There was no significant difference in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP) between the two groups. Health Assessment Questionnaire for Spondyloarthropathies (HAQ-s) showed that Yisaipu® group was superior to original biological group in terms of eating, gripping and driving. In addition, the medical cost of Yisaipu® was lower than that of original biologicals. The overall impact of the COVID-19 epidemic on patients of original biological group was comparatively smaller than that on Yisaipu® group.

Abbreviations: ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score-CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reaction protein; HAQ-S, Health Assessment Questionnaire for Spondyloarthropathies; NA, not available; PGA, Patient's Global assessment; USD, USA dollar.

Conclusions: Yisaipu® provided AS patients with an economical selection during regular follow-up, while original biologicals had certain advantages in the COVID-19 epidemic setting, including a longer time interval between two drug administrations and the self-injection dose form of medication.

Keywords: ankylosing spondylitis (AS), cost-effectiveness, COVID-19, Yisaipu®, original biologicals

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic autoimmune disease mainly affecting the axial skeleton with the main clinical manifestation of inflammatory lower back pain. AS can simultaneously involve the peripheral joints and extraarticular tissues, presenting as peripheral arthritis, enthesitis, ophthalmitis (mostly acute uveitis) and intestinal inflammation (Sieper and Poddubnyy, 2017). The disease is more likely to occur in young men, seriously affecting their quality of life (QOL) and working capability. In addition, AS may need a long-term course of treatment, which is a huge economical burden on individuals, families and society.

Anti-TNF therapy represents a milestone in the treatment of AS in that biologicals act fast, safely and effectively. The European League Against Rheumatism (EULAR), the Assessment of Spondylarthritis International Society (ASAS) and the American College of Rheumatology (ACR) guidelines recommend biologicals as the first line drugs for AS (Van der Heijde et al., 2017; Ward et al., 2019). Original biologicals, Infliximab (IFX) (5 mg/kg intravenous injection on week 0, week 2, week 6, once every 6 wk), Adalimumab (ADA) (40 mg once 2 wk subcutaneous injection), Golimumab (GLM) (50 mg once 4 wk subcutaneous injection)and Etanercept (ETN) (25 mg twice a week subcutaneous injection) have been approved for the treatment of AS in China. The monthly cost of full-dose administration of original biologicals averaged 3000–4000 CNY (441–588 USD), which was obviously expensive against 28,228 CNY (4151 USD) of the annual disposable income per capita (2018) in China (2019). It is generally accepted that economic factor to some extent limits the use of original biologicals in some AS patients. Yisaipu® a biosimilar for ETN (25 mg twice a week subcutaneous injection), was most commonly used for the treatment of AS in China (Dongbao Zhao et al., 2021). As a tumor necrosis factor (TNF) receptor fusion protein, Yisaipu® was marketed in 2005 and entered Shanghai Medical Insurance System in the same year (Scheinberg and Kay, 2012). According to the age and the state of employment of AS patients, 50–80% of the Yisaipu® cost could be covered by the Medical Insurance in Shanghai, and as a result the month full-dose Yisaipu® administration fee incurred by an individual patient was about 500–1000 CNY (73.5 USD~147 USD). Compared with the original biologicals, the use of Yisaipu® can greatly reduce the economic burden on AS patients so that more AS patients can afford to receive effective treatment. Although results from RCTs found out that biosimilar benefits AS patients (Xu et al., 2019), the questions whether Chinese medical insurance should cover original biologicals, or if original biologicals have more advantages than Yisaipu® in real world remain unclear.

We started to establish AS patient cohort since 2016 to provide the patients regular visits, and to setup clinical database. China was the first country where COVID-19 epidemic started (Liu et al., 2020). The ongoing COVID-19 pandemic remains an important healthcare challenge for patients with chronic disease. We were very fortunate to keep in contact with most of the patients in our established through COVID-19 epidemic. We collected data of disease activity, adverse event, compliance and impact of COVID-19 epidemic on treatment of AS patients. We believed that the data of our established cohort through COVID-19 epidemic added great value to long term management of AS patients.

MATERIALS AND METHODS

Included in this study were all AS patients who received original biologicals or Yisaipu® in our center and had been regularly followed up for more than a year before October 2019. All the included patients met the modified New York criteria (1984) for ankylosing spondylitis (Van der Linden et al., 1984). Before using original biologicals or Yisaipu®, they all had undergone regular screening tests for tuberculosis (TB), hepatitis and tumors. Treatment of AS was based on a shared decision between the patients and the rheumatologists. We collected six questions that rheumatologists and patients were concerned about when considering the use of aTNF's (therapeutic effect, cost, safety, drug tapering and discontinuation, interval of drug administration, methods of administration). We recorded and analyzed the three most important questions choosed by rheumatologists and patients. We collected data on adverse events from two sources. One was patient's report, and the other was laboratory tests or medical instrument exam results. After recording AE, rheumatologists evaluated the severity of AE and judged whether AE was related to biologicals. All data of cost were collected from patients report. As the proportion of Chinese medical insurance coverage varied according to the age and working status of patients, it was difficult to get accurate data of cost from physicians' clinics. IFX and Yisaipu® must be administered in our clinic, while ETN, ADA and GLM can be injected by patients themselves. Rheumatologists made appointment of next visit with patients in daily clinics, but no reminder would be sent to patients in regular practice in China. Patients' data included their general and demographic characteristics, disease activity, BASDAI, ASDAS-CRP, Patient's Global assessment (PGA), QOL, medical compliance, income levels and expenditures. QOL was assessed by Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S) (Zochling, 2011), including dressing, arising, eating, walking, hygiene, reaching, gripping, activities, desk job and driving, totaling 10 dimensions. Compliance was assessed by Compliance Questionnaire-Rheumatology (CQR) including 19

TABLE 1 | Patient demographic characteristics and clinical manifestations.

		Original Biologicals (*n* = 41)	Yisaipu® (*n* = 178)	*p* value
Age (yr)		35.8 ± 12.4	38.0 ± 10.8	0.132
Sex (male) (*n*, %)		35 (85.4)	156 (87.6)	0.694
Marriage (*n*, %)	Unmarried	14 (34.1)	42 (23.6)	0.304
	Divorced	1 (2.4)	2 (1.1)	
	Widowed	0 (0.0)	2 (1.1)	
	Married	26 (63.4)	132 (74.2)	
Income (USD/year) (*n*, %)	<7,352.9	26 (63.4)	45 (25.3)	<0.001[a]
	7,352.9–14,705.9	13 (31.7)	59 (33.1)	
	14,705.9–29,411.8	2 (4.9)	46 (25.8)	
	>29,411.8	0 (0.0)	28 (15.7)	
Education level (*n*, %)	Primary school	2 (4.9)	4 (2.2)	0.153
	Junior school	11 (26.8)	32 (18.0)	
	High school	14 (34.1)	45 (25.3)	
	College	13 (31.7)	85 (47.8)	
	Master	1 (2.4)	12 (6.7)	
Duration (yr)		11.3 ± 8.9	10.7 ± 7.9	0.815
Follow-up (yr)		3.1 ± 2.2	3.3 ± 2.8	0.553
Cost (USD/mo)		340.2 ± 279.8	174.1 ± 117.4	<0.001[a]
CRP (mg/dl)		16.4 ± 21.2	10.6 ± 14.1	0.049[b]
BASDAI		3.3 ± 2.3	3.1 ± 1.9	0.772
ASDAS-CRP		1.9 ± 0.9	1.8 ± 0.7	0.776
PGA		3.0 ± 0.7	2.9 ± 0.8	0.808
HAQ-S	Mean	0.5 ± 0.6	0.4 ± 0.5	0.102
	Dressing	0.5 ± 0.7	0.4 ± 0.8	0.354
	Arising	0.6 ± 0.8	0.4 ± 0.7	0.087
	Eating	0.2 ± 0.6	0.1 ± 0.3	0.017[b]
	Walking	0.6 ± 0.9	0.5 ± 0.8	0.238
	Hygiene	0.4 ± 0.7	0.3 ± 0.7	0.052
	Reaching	0.8 ± 0.9	0.6 ± 0.9	0.066
	Gripping	0.3 ± 0.6	0.1 ± 0.5	0.004[b]
	Activities	0.8 ± 1.0	0.4 ± 0.7	0.099
	Driving	1.4 ± 1.0	0.9 ± 0.9	0.001[b]
	Desk job	1.0 ± 0.9	0.9 ± 0.8	0.612
Extra-articular manifestations (*n*, %)	Uveitis	5 (12.2)	30 (16.9)	<0.001[a]
	IBD	4 (9.8)	0 (0.0)	
	Psoriasis	3 (7.3)	2 (1.1)	
	None	29 (70.7)	146 (82.0)	
T-Spot (*n*, %)	Positive	0 (0.0)	26 (14.6)	0.019[b]
HBsAg (*n*, %)	Positive	0 (0.0)	10 (5.6)	0.255
Age-appropriate for work		34	157	NA
Employed (*n*, %)		18 (52.9)	143 (91.1)	<0.001[a]

[a]p < *0.001*.
[b]p < *0.05*.

questions (De Klerk et al., 1999). In addition, the patients were also asked about whether they omitted or misused the drug, reasons for omitting or misusing the drug. Cost of anti-TNF treatment was also recorded according to patients' report.

The pre-COVID-19 data were collected between Aug, 2019 to Oct, 2019, and the post-COVID-19 data were collected between Mar, 2021 to Apr, 2021 from regular face-to- face visits. The data during COVID-19 were collected by telephone interviews from April

TABLE 2 | Adverse events of patients.

	Original Biologicals (*n* = 41)	Yisaipu® (*n* = 178)
Upper respiratory infection (*n*, %)	ENT 1 (2.4) ADA 1 (2.4) GLM 1 (2.4) IFX 3 (7.3)	25 (14.0)
Pneumonia (*n*, %)	IFX 1 (2.4)	3 (1.7)
Herpes Zoster (*n*, %)	GLM 1 (2.4)	1 (0.6)
Injection site reaction (*n*, %)	ENT 1 (2.4)	27 (15.2)
Abnormal liver function (*n*, %)	IFX 1 (2.4) GLM 1 (2.4)	15[a] (8.4)
Two or more AE (*n*, %)	IFX 1 (2.4) ADA 1 (2.4)	7 (3.9)

AE, adverse effect.
[a]*Two of which with a combination of isoniazid.*

TABLE 3 | Compliance of patients.

	Original Biologicals (*n* = 41)	Yisaipu® (*n* = 178)	*p* value
CQR	71.4 ± 10.9	70.5 ± 12.0	0.753
Omitting or misuse the drug	22 (53.6)	55 (30.9)	0.006*
Reasons for omitting or misusing the drug			
Forget to use the drug	12 (29.3)	35 (19.7)	NA
Changing drug administration frequency spontaneously	12 (29.3)	23 (12.9)	NA
Mis-remembering the time of drug administration	0 (0)	4 (2.2)	NA
No drug available	0 (0)	12 (6.7)	NA
Using a device to remind drug administration	6 (14.6)	23 (12.9)	NA

NA, not available.

20th to 27th, 2020. Patients were asked about the overall impact of the epidemic on them including change in the frequency of drug administration, using visual analogue scale (VAS). We defined 0 as no influence, and 10 as great influence of epidemic so that the patient could not continue therapy. The study closely followed the principles of the Declaration of Helsinki and was approved by ethics committee of the Second Military Medical University, and all patients provided written informed consent.

All obtained data were analyzed by SPSS 21.0. Continuous variables were expressed as mean ± standard deviation while categorical variables were expressed as frequency (composition ratio). Comparison between groups of normally distributed continuous variables was conducted by independent sample *t* test; comparison between two groups of continuous variables with non-normal distribution was conducted by Wilcoxon sign rank test. Chi-square test was used to compare categorical variables between the two groups. Values of $p < 0.05$ were considered statistically significant.

RESULTS

This study included 219 patients, of whom 41 patients received original biologicals including ENT ($n = 4$), IFX ($n = 28$), ADA ($n = 8$) and GLM ($n = 1$), and 178 patients received the Yisaipu®. There was no significant difference in age, sex between patients using original biologicals and those using Yisaipu®, nor was there significant difference in BASDAI and ASDAS-CRP between the two groups, excepted that C-reactive protein (CRP) of Yisaipu® group was lower than that of original biological group (10.6 ± 14.1 *vs* 16.4 ± 21.2). The treatment cost for anti-TNF treatment in Yisaipu® group was significantly lower than that in original biological group (174.1 ± 117.4 *vs* ± 340.2 ± 279.8). The result of HAQ-S suggested that Yisaipu® group was superior to original biological group in eating (0.1 ± 0.3 *vs* 0.2 ± 0.6), gripping (0.1 ± 0.5 *vs* 0.3 ± 0.6) and driving (0.9 ± 0.9 *vs* 1.4 ± 1.0) (**Table 1**). With respect to safety, no severe adverse event occurred throughout the treatment period in both groups. The main adverse events in original biological group and Yisaipu® group were upper respiratory tract infection (14.5% *vs* 14.0%), pulmonary infection (2.4% *vs* 1.7%), herpes zoster (2.4% *vs* 0.6%), injection site reaction (2.4% *vs* 15.2%), and liver enzyme elevation (4.8% *vs* 8.4%) (**Table 2**).

With respect to compliance, there was no significant difference in the compliance questionnaire of rheumatology (CQR) between the two groups. There were cases of omitting or misusing the drugs in the original biological group *vs* Yisaipu® group (22, 53.6% *vs* 55, 30.9%). The main reasons for omitting or misusing the drugs were forgetting to use the drug (12, 29.3% *vs* 35, 19.7%), changing the frequency of drug administration spontaneously

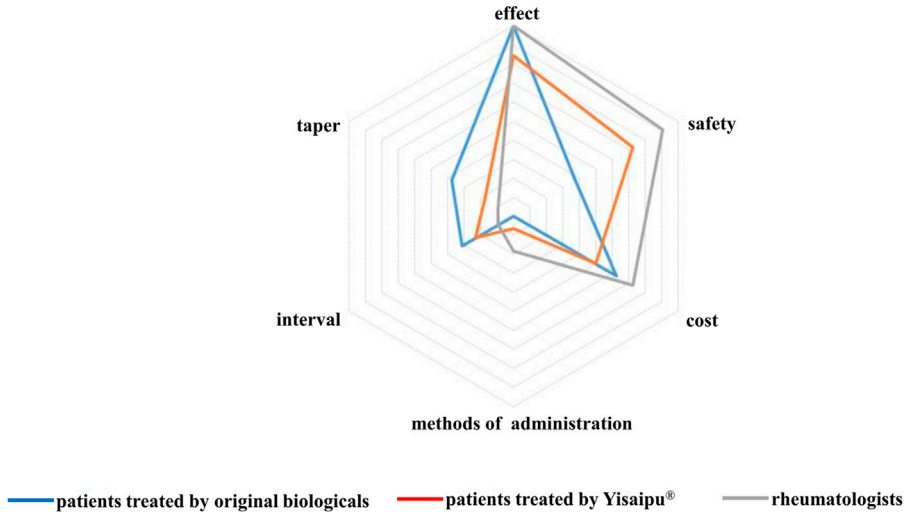

FIGURE 1 | Concerned problems in original biological and Yisaipu® groups, The most concerned problems in original biological group were the therapeutic effect (41, 100%), cost (25, 61.0%), safety (15, 36.6%), drug tapering and discontinuation (15, 36.6%), interval of drug administration (13, 31.7%), route of drug administration (0, 0%). The most concerned problems in Yisaipu® group were the therapeutic effect (150, 84.3%), safety (129, 72.5%), cost (90, 50.6%), interval of drug administration (41, 23.0%), drug tapering and discontinuation (31, 17.4%), and route of drug administration (12, 6.7%). The most concerned issues of the rheumatologists were the therapeutic effect (11, 100%), safety (10, 90.9%), cost (8, 72.7%), way of injection (2, 18.2%), interval of drug administration (1, 9.1%), and drug tapering and discontinuation (1, 9.1%).

TABLE 4 | Impact of COVID-19 on patient treatment.

	Original Biologicals (*n* = 41)	Yisaipu® (*n* = 150)	*p* value
VAS	2.9 ± 2.8	5.2 ± 2.9	<0.001[a]
Withdrawal (*n*, %)	7 (17.1)	50 (33.3)	0.044[b]
No change in frequency (*n*, %)	33 (80.5)	44 (29.3)	<0.001[a]
2/3 of primary frequency (*n*, %)	0 (0)	20 (13.3)	NA
1/2 of primary frequency (*n*, %)	1 (2.4)	27 (18.0)	NA
Less than 1/2 of primary frequency (*n*, %)	0 (0)	9 (6.0)	NA

[a]p < *0.001*.
[b]p < *0.05*.

(12, 29.3% *vs* 23, 12.9%), mistaking the time of drug administration (0, 0% *vs* 4, 2.2%), and having no drugs (0, 0% *vs* 12, 6.7%). The proportion of patients who used a device to remind them of drug administration was relatively low in both groups (6, 14.6% *vs* 23, 12.9%) (**Table 3**).

The most concerned problems in original biological group were the therapeutic effect (41, 100%), cost (25, 61.0%), safety (15, 36.6%), drug tapering and discontinuation (15, 36.6%), interval of drug administration (13, 31.7%), route of drug administration (0, 0%). The most concerned problems in Yisaipu® group were the therapeutic effect (150, 84.3%), safety (129, 72.5%), cost (90, 50.6%), interval of drug administration (41, 23.0%), drug tapering and discontinuation (31, 17.4%), and route of drug administration (12, 6.7%). The most concerned issues of the rheumatologists were the therapeutic effect (11, 100%), safety (10, 90.9%), cost (8, 72.7%), way of injection (2, 18.2%), interval of drug administration (1, 9.1%), and drug tapering and discontinuation (1, 9.1%) (**Figure 1**).

From April 20th to 27th, 2020, we made telephone interviews with the 41 patients in original biological group and 150 patients in Yisaipu® group. Of the 178 patients originally enrolled in Yisaipu® group, 15 were unable to be contacted by telephone, five male patients and a female patient discontinued the drug for preparing pregnancy, five patients converted to original biological therapy, and two patients discontinued the drug because of upper respiratory tract infection. We evaluated the effect of COVID-19 on the treatment of AS patients from two aspects. One was subjective effect, referring to VAS of impact of epidemic on the treatment. The other was the effect on disease activity (BASDAI, PGA). We found significant difference in subjective effect (**Table 4**). Compared with Yisaipu® group, the impact on original biological group was relatively small in terms of the visual analogue score (VAS) of patients who personally reported that the epidemic affected their treatment (2.9 ± 2.8 *vs* 5.2 ± 2.9); the proportion of patients who discontinued the use of the drug was relatively low (17.1% *vs* 33.3%), and the percentage of

TABLE 5 | Disease activity through COVID-19 epidemic.

	Original Biologicals				Yisaipu®			
	Period 1 (*n* = 41)	Period 2 (*n* = 41)	Period 3 (*n* = 41)	*p* value	Period 1 (*n* = 178)	Period 2 (*n* = 150)	Period 3 (*n* = 160)	*p* value
PGA	3.0 ± 0.7	3.3 ± 1.0	2.9 ± 0.7	NS	2.9 ± 0.8	3.1 ± 1.2	3.1 ± 0.9	NS
BASDAI	3.2 ± 2.3	3.2 ± 1.6	2.8 ± 1.1	NS	3.1 ± 1.9	3.1 ± 1.3	3.0 ± 1.1	NS
CQR	71.4 ± 10.9	-	71.0 ± 9.5	NS	70.5 ± 12.0	-	72.0 ± 11.1	NS

Period 1: pre-COVID-19, Aug-Oct 2019; Period 2: COVID-19, Apr 20th–27th 2020; Period 3: post- COVID-19, Mar-Apr 2021; NS, no significance.

patients who maintained the regular frequency of drug administration was also high (80.5% *vs* 29.3%). As for the impact on disease activity, we did not find significant difference in BASDAI and PGA before, during and after COVID-19 epidemic in both groups. As majority of AS patients did not attend hospital during COVID-19 epidemic, comprehensive CQR data during COVID-19 epidemic were not available. Significant difference was fail to be found in CQR before and after COVID-19 epidemic in both groups (**Table 5**).

DISCUSSION

The present study showed that the proportion of patients who received Yisaipu® was significantly higher than that of patients who received original biologicals (81.3% *vs* 18.7%), which leaded to a major difference in number of patients between two groups. This is most probably because Yisaipu® has been covered by the national and Shanghai medical insurance systems since 2005. As long-term treatment is required for AS, the treatment cost is an important factor that determines what drug AS patients prefer to use. It was found in our study that more than 50% patients in both groups were concerned about the treatment cost when they made a decision to choose original biologicals or Yisaipu® (61.0% *vs*50.6%). The Task Force on the Use of Biosimilars to Treat Rheumatological Diseases (2018) pointed out that the medical insurance system, economic factors and other contextual aspects of the patients should be fully considered when original biologicals or biosimilars were chosen (Jonathan Kay et al., 2018). In the present study, the cost of Yisaipu® used in our patients was covered proportionally by the insurance reimbursement sponsored by the government. While the cost of original biologicals was mainly paid by the patients personally or the families. For this reason, the medical cost of Yisaipu® group was significantly lower than that of original biological group. In addition, patients in original biological group were more concerned about drug tapering and discontinuation (36.6% *vs* 17.4%) and intervals between doses (31.7% *vs* 23.0%), which may also be a reason for the higher cost of using original biologicals.

The therapeutic effect was an issue that the patients in original biological group and Yisaipu® group groups were concerned about (100% *vs* 84.3%). All patients consulted whether inactive disease or moderate disease activity could be achieved by original biologicals or Yisaipu® before the decision was made. It was found in our study that there was no significant difference in BASDAI, PGA and ASDAS-CRP between two groups. However, the mean CRP level in Yisaipu® group was significantly lower than that in original biological group. The result of HAQ-S suggested that Yisaipu® group was superior to original biological group in eating, gripping and driving. The result of working-related questionnaire showed that Yisaipu® group was superior to original biological group in terms of work performance and income level. This may be due to the higher rate of drug omitting or misusing in original biological group as compared with Yisaipu® group (53.6% *vs* 30.9%). These results suggested that the therapeutic effect of Yisaipu® was no weaker than that of original biologicals in regular and long-term follow-up patients, and that adequate treatment with Yisaipu® facilitates controlling the disease and resuming normal work on the part of the patients. The proportion of extraarticular manifestations in patients using original biologicals was higher than that of patients using Yisaipu®. The reason may be thatYisaipu® is an TNF receptor fusion protein, while the therapeutic effect of monoclonal antibody anti-TNF agents on extraarticular manifestations such as psoriasis, uveitis and inflammatory bowel disease is better than that of TNF receptor fusion protein. With further research and development of biosimilars, monoclonal antibody biosimilars will be gradually applied to clinical use. The latest randomized double-blind controlled trial has demonstrated that the therapeutic effect, safety and immunogenicity of the biosimilar IBI301 was highly similar to those of ADA in the treatment of AS patients (Xu et al., 2019). We hope that commercial availability of these biosimilars would provide more economical therapeutic alternatives for AS patients who are complicated with extraarticular manifestations.

It was found in our study that there was a certain proportion of patients who omitted or misused the drugs in both groups. The reasons for omitting or misusing the drugs included forgetting to administer the drugs, spontaneously changing the frequency of drug administration, and mis-remembering the time of drug administration. AS is a chronic disease which need long term therapy. However, the standard chronic disease management system is still lacking. In most clinics in China, there is no nurse to remind patients for their regular visits. Some patients cancelled appointment spontaneously due to different reasons, so the frequency of drug administration was changed sometimes. The proportion of patients who used a device to remind them of the ratio of medication was relatively low in both groups. Therefore, we speculated that chronic disease management was of great importance for AS patients, and it was necessary

to follow up patients regularly, provide patients education, and give them suggestions of using a notebook, calendar and alarm clock to remind them of the time of drug administration for the sake of helping them use the drugs accurately and in time. Several factors influenced the compliance of AS patients. Firstly, we did not have reminders for patients. Secondly, there were always too many patients in daily clinics, and the so that it would take patients about at least 2–3 h for each follow up. Thirdly, some patients had insurance problems after they lose their jobs. All these factors had impact on patient's compliance. So we did not speculate that the drug had to be administered within hospital compliance was always better as compared to self administered in China.

Safety was also an issue that patients in both groups concerned about. It was found that safety was an important factor affecting the persistence of TNF inhibitor therapy (Roberto; Marchesoni et al., 2009; Caporali et al., 2018). The adverse effects of TNF inhibitors mainly included infection, increased risk of TB and hepatitis B virus (HBV) infection, injection site reaction, abnormal liver function, severe allergic reaction, autoimmune disease, new onset of psoriasis, and tumors (Fouache et al., 2009; Maxwell et al., 2015; Ramiro et al., 2017; Webers et al., 2019). China was one of the 22 countries and regions with high TB burdens, and the annual incidence of TB infection in China accounts for about 10% of the total global cases (Guo et al., 2017). The prevalence of hepatitis B in China was about 5.49%, totaling about 74.60 million people (Aparna Schweitzer et al., 2015). For this reason, all AS patients need to undergo strict screenings for hepatitis B and TB before receiving original biologicals or Yisaipu®. Not a single patient in the original biological group was found positive for T-spot and HBsAg. It was reported that TNF monoclonal antibodies may more strongly inhibit granuloma formation in tuberculosis as compared with etanercept (Takahiko Horiuchi et al., 2010). So doctors tend to suggest the use of TNF receptor fusion protein (Yisaipu® or ETN) instead of monoclonal antibody original biologicals (ADA, IFX, GLM) in patients with positive T-spot and HBsAg for safety consideration. Abnormal liver function was found in 15 patients treated with Yisaipu®, two of which with a combination of isoniazid. We did not observe the newly diagnosed malignant tumor during the treatment. Data from the Swedish (Anti-Rheumatic Therapy in Sweden (ARTIS)) and Danish (DANBIO) biologics registers (ARTIS = 5448, DANBIO = 3255) indicated that treatment with aTNF was not associated with increased risks of cancer [Karin Hellgren et al., 2017]. The patients in our cohort were relatively young. We will document the data of malignancy in larger population and longer follow-up. We recorded all the adverse events, but we didn't find severe adverse event during follow up. Most of AEs such as injection site reaction or abnormal liver function in our cohort were mild and transient, we monitored clinical and laboratory test result and continue drug administration. For infections, such as upper respiratory infection with fever or pneumonia, we stopped biological treatment, and started treatment again after infection recovery. No severe adverse event occurred in our study. The overall incidence of adverse events was relatively low, while the safety and tolerance rates were relatively high in both groups. This may be due to the strict screening before initiation of the biological or biosimilar therapy in our center. The prevalence of AE was similar to other studies [Paras Karmacharya et al., 2020]. We speculated that the prevalence of AE was relatively low both in original biologicals and Yisaipu® group after regular checkups. We will keep on visit and record AE during follow up to accumulate more data on safety in real world practice.

China was the first country where Covid 19 epidemic started. The ongoing COVID-19 pandemic remains an important healthcare challenge, especially for chronic diseases. But the exact data is still scarce. Since the COVID-19 epidemic outbreaked in December 2019, the formalities for outpatient visits and hospital admission had been enhanced in accordance with the quarantine requirements, which to some extent increased the inconvenience of patients coming to the hospital. In addition, some patients feared that coming to hospital would increase the risk of being infected. Furthermore, patients' relatives, friends or colleagues advised them not to go to hospital because of their fear to get virus. All these factors posed an impact on the original biological or Yisaipu® therapy of AS patients. We were very fortunate to keep in contact with most of the patients in our established and stable cohort during and after COVID-19 epidemic. The results of our telephone interviews of the AS patients under long-term follow-up observation in our department showed that COVID19 produced some impact on the treatment of patients receiving original biologicals or Yisaipu®. Compared with Yisaipu® group, the impact on original biological group was relatively small. With respect to the frequency of drug administration, the proportion of patients who discontinued drug administration in original biological group was lower than that in Yisaipu® group, and the proportion of patients who maintained the required frequency of drug administration was also higher. This may be due to the following two reasons. On the one hand, patients using Yisaipu® and IFX had to attend hospital to get their injections. As Yisaipu® was not PFS and IFX needed to be injected intravenously, both Yisaipu® and IFX cannot be injected by patients themselves. Nurses in China did not provide injection treatment in patient's home. So these patients had to attend hospital to get their injections. While original biologicals, including ETN, ADAa and GLM were PFS, which can be self administered by patients themselves, which reduces the impact of drug administration on the therapeutic outcome. On the other hand, although patients receiving Infliximab needed to go to the hospital for the prescription, the interval between two drug administrations was relatively long and therefore the impact on the therapeutic outcome was relatively small within a certain period. We did not find significant increase in BASDAI, PGA during COVID-19 epidemic. This may due to a series of measures taken by the Chinese government, which made the impact of COVID-19 on regular medical services lasted for a short period of time. It is our hope that there would be self-injection dose forms for biosimilars in the near future. Commercial availability of TNF monoclonal antibody biosimilars would bring about more

convenience to AS patients. The medical insurance list in China has been under yearly adjustment according the requirement of the patients, and some original biologicals have gradually entered the lists of the national and regional medical insurance systems. In addition, the prices of original biologicals and biosimilars are on the decline. We hope that all these measures and policies would help to provide AS patients with more alternatives to choose safer and more effective, economical and convenient original biologicals or biosimilars.

This study has some limitations. First, the sample size is relatively small. We still lack standard chronic disease management system in our country, and patients loss to follow up or discontinue treatment due to economic consideration, poor compliance and ineffective therapeutic outcomes or intolerability due to adverse events. Some patients went to other hospitals for continuous treatment. We have realized the importance of chronic disease management. Our ongoing work will explore causes of patients who are unable to maintain regular long-term follow-ups, in an attempt to seek better ways for chronic disease management of AS patients. Second, the original biologicals used in this study were ENT, IFX, ADA and GLM, and tYisaipu®. Of them, ENT and Yisaipu® are receptor fusion proteins of TNF-a, while IFX, GLM and ADA are mono-clonal antibodies of TNF-a. Although they are all TNF-a inhibitors and therefore have similar action mechanisms, there are some differences in the structure, pharmacokinetics, and frequency and method of administration between these drugs. In China, there are Geleli®, Anjianning®, Sulixin® (all biosimilars for ADA) registered after 2018. Geleli® has been included in Chinese medical insurance in 2021. With further research and development of biosimilars, monoclonal antibody biosimilars will be gradually applied to clinical use. We will make further comparisons between the clinical data of biosimilars and their bio-originator.

There are more than 5 million AS patients in China, and the demand for anti-TNF therapy is huge. Majority of AS patients in China chose to receive biosimilar treatment considering of economic factors. So China is one of the largest markets for biosimilar. Previous RCTs have pointed out the effectiveness and safety of biosimilar, however, the data of long - term use in real world is still scarce. The data of our cohort in regular visits and through COVID-19 will add real value to chronic disease management and to the development of biosimilar in China. Although the data from regular visits indicated that there were no significant differences between original biological and Yisaipu® group in effectiveness and safety, our result showed that the overall impact of the COVID-19 epidemic on original biological group was comparatively smaller than Yisaipu® group. We speculate that the development of PFS and longer injection interval biosimilar will benefit AS patients during specific circumstances such as COVID-19.

CONCLUSION

In summary, the medical insurance system in China has provided AS patients with more economical therapeutic alternatives. However, original biologicals do have some advantages under the special circumstance of COVID-19, We speculate that the longer intervals and PFS may provide convenience to AS patients during COVID-19.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Shanghai Changzheng hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HX, TL, HL, YW, and XWa conceived and conducted the study. TL, HL, YW, and XWa analysed, interpreted the data, and participated in drafting manuscript. HX, TL, and HL revised the manuscript. XWu, LZ, LL, RS, and HT made substainal contributions to the participant recruitment and data collection. All the authors read and approved the final manuscript.

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REFERENCES

Caporali, R., Crepaldi, G., Codullo, V., Benaglio, F., Monti, S., Todoerti, M., et al. (2018). 20 Years of Experience with Tumour Necrosis Factor Inhibitors: What Have We Learned? *Rheumatology (Oxford)* 57 (Suppl. 7), vii5. doi:10.1093/rheumatology/key059

China National Bureau of Statistics (2019). *China Statistics Yearbook*.

De Klerk, E., van der Heijde, D., van der Tempel, H., and van der Linden, S. (1999). Development of a Questionnaire to Investigate Patient Compliance with

Antirheumatic Drug Therapy. *J. Rheumatol.* 26 (12), 2635–2641. doi:10.1097/00124743-199912000-00020

Fouache, D., Goeb, V., Massy-Guillemant, N., Avenel, G., Bacquet-Deschryver, H., Kozyreff-Meurice, M., et al. (2009). Paradoxical Adverse Events of Anti-tumour Necrosis Factor Therapy for Spondyloarthropathies: A Retrospective Study. *Rheumatology (Oxford)* 48 (7), 761–764. doi:10.1093/rheumatology/kep083

Guo, C., Du, Y., Shen, S. Q., Lao, X. Q., Qian, J., and Ou, C. Q. (2017). Spatiotemporal Analysis of Tuberculosis Incidence and its Associated Factors in Mainland China. *Epidemiol. Infect.* 145 (12), 2510–2519. doi:10.1017/S0950268817001133

Hellgren, K., Dreyer, L., Arkema, E. V., Glintborg, B., Jacobsson, L. T., Kristensen, L. E., et al. (2017). Cancer Risk in Patients with Spondyloarthritis Treated with TNF Inhibitors: A Collaborative Study from the ARTIS and DANBIO Registers. *Ann. Rheum. Dis.* 76 (1), 105–111. doi:10.1136/annrheumdis-2016-209270

Horiuchi, T., Mitoma, H., Harashima, S., Tsukamoto, H., and Shimoda, T. (2010). Transmembrane TNF-Alpha: Structure, Function and Interaction with Anti-TNF Agents. *Rheumatology (Oxford)* 49 (7), 1215–1228. doi:10.1093/rheumatology/keq031

Karmacharya, P., OgdieShahukhal, A., and Alexis, O., (2020). Risk of Malignancy in Spondyloarthritis: A Systematic Review. *Rheum. Dis. Clin. North. Am.* 46 (3), 463–511. doi:10.1016/j.rdc.2020.04.001

Kay, J., Schoels, M. M., Dörner, T., Emery, P., Kvien, T. K., and Breedveld, J. S. F. C. (2018). Consensus-based Recommendations for the Use of Biosimilars to Treat Rheumatological Diseases. *Ann. Rheum. Dis.* 77 (2), 165–174. doi:10.1136/annrheumdis-2017-211937

Liu, W., Zhang, Q., Chen, J., Xiang, R., Song, H., Shu, S., et al. (2020). Detection of Covid-19 in Children in Early January 2020 in Wuhan, China. *N. Engl. J. Med.* 382 (14), 1370–1371. doi:10.1056/NEJMc2003717

Marchesoni, A., Zaccara, E., Gorla, R., Bazzani, C., Sarzi-Puttini, P., Atzeni, F., et al. (2009). TNF-alpha Antagonist Survival Rate in a Cohort of Rheumatoid Arthritis Patients Observed Under Conditions of Standard Clinical Practice. *Ann. N. Y Acad. Sci.* 1173, 837–846. doi:10.1111/j.1749-6632.2009.04621.xNYAS4621

Maxwell, L. J., Zochling, J., Boonen, A., Singh, J. A., Veras, M. M., Tanjong Ghogomu, E., et al. (2015). TNF-alpha Inhibitors for Ankylosing Spondylitis. *Cochrane Database Syst. Rev.* 4, CD005468. doi:10.1002/14651858.CD005468.pub2

Ramiro, S., Sepriano, A., Chatzidionysiou, K., Nam, J. L., Smolen, J. S., van der Heijde, D., et al. (2017). Safety of Synthetic and Biological DMARDs: A Systematic Literature Review Informing the 2016 Update of the EULAR Recommendations for Management of Rheumatoid Arthritis. *Ann. Rheum. Dis.* 76 (6), 1101–1136. doi:10.1136/annrheumdis-2016-210708

Regel, A., Sepriano, A., Baraliakos, X., van der Heijde, D., Braun, J., Landewé, R., et al. (2017). Efficacy and Safety of Non-pharmacological and Non-biological Pharmacological Treatment: A Systematic Literature Review Informing the 2016 Update of the ASAS/EULAR Recommendations for the Management of Axial Spondyloarthritis. *RMD Open* 3 (6), e000397. doi:10.1136/rmdopen-2016-000397

Scheinberg, M. A., and Kay, J. (2012). The Advent of Biosimilar Therapies in Rheumatology--"O Brave New World". *Nat. Rev. Rheumatol.* 8 (7), 430–436. doi:10.1038/nrrheum.2012.84

Schweitzer, A., Horn, J., Mikolajczyk, R. T., Krause, G., and Ott, J. J. (2015). Estimations of Worldwide Prevalence of Chronic Hepatitis B Virus Infection: A Systematic Review of Data Published between 1965 and 2013. *Lancet* 386 (10003), 1546–1555. doi:10.1016/S0140-6736(15)61412-X

Sieper, J., and Poddubnyy, D. (2017). Axial Spondyloarthritis. *Lancet* 390 (10089), 73–84. doi:10.1016/S0140-6736(16)31591-4

Van der Linden, S., Valkenburg, H. A., and Cats, A. (1984). Evaluation of Diagnostic Criteria for Ankylosing Spondylitis. A Proposal for Modification of the New York Criteria. *Arthritis Rheum.* 27 (4), 361–368. doi:10.1002/art.1780270401

Ward, M. M., Deodhar, A., Gensler, L. S., Dubreuil, M., Yu, D., Khan, M. A., et al. (2019). 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Care Res. (Hoboken)* 71 (10), 1285–1299. doi:10.1002/art.4104210.1002/acr.24025

Webers, C., Vanhoof, L., Leue, C., Boonen, A., and Köhler, S. (2019). Depression in Ankylosing Spondylitis and the Role of Disease-Related and Contextual Factors: A Cross-Sectional Study. *Arthritis Res. Ther.* 21 (1), 215. doi:10.1186/s13075-019-1995-7

Xu, H., Li, Z., Wu, J., Xing, Q., Shi, G., Li, J., et al. (2019). IBI303, a Biosimilar to Adalimumab, for the Treatment of Patients with Ankylosing Spondylitis in China: A Randomised, Double-Blind, Phase 3 Equivalence Trial. *Lancet Rheumatol.* 1 (1), e35–e43. doi:10.1016/s2665-9913(19)30013-x

Zhao., D., He, D., Bi., L., Wu., H., Liu, Y., Wu., Z., et al. (2021). Safety and Efficacy of Prefilled Liquid Etanercept-Biosimilar Yisaipu for Active Ankylosing Spondylitis: A Multi-Center Phase III Trial. *Rheumatol. Ther.* 8, 361–374. doi:10.1007/s40744-021-00276-1

Zochling, J. (2011). Measures of Symptoms and Disease Status in Ankylosing Spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res. (Hoboken)* 63 (Suppl. 11), S47–S58. doi:10.1002/acr.20575

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Key Determinants of Health-Related Quality of Life Among Advanced Lung Cancer Patients: A Qualitative Study in Belgium and Italy

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Background: The lung cancer (LC) treatment landscape has drastically expanded with the arrival of immunotherapy and targeted therapy. This new variety of treatment options, each with its own characteristics, raises uncertainty regarding the key aspects affecting patients' health-related quality of life (HRQL). The present qualitative study aimed to investigate how LC patients perceive their HRQL and the factors that they consider to be most influential in determining their HRQL.

Methods: This qualitative research incorporates four focus group discussions, with six LC patients in each group. In total, 24 stage III and IV LC patients were included in the discussions, with Italian (n = 12) and Belgian (n = 12) patients, age range: 42–78, median age = 62 (IQR = 9.3 years), SD = 8.5; 62% men. Using thematic analysis, transcripts and notes from the FGDs were analyzed using NVivo software (edition 12).

Results: Three main themes capturing determinants of HRQL were identified. First, patients agreed on the importance of physical aspects (symptoms and side-effects) in determining their HRQL. In particular, skin conditions, nausea, fatigue, risk of infections, sensory abnormalities, pain, and changes in physical appearance were highlighted. Second, patients worried about psychological aspects, negatively impacting their wellbeing such as uncertainties regarding their future health state, and a lower degree of autonomy and independence. Third, patients underlined the importance of social aspects, such as communication with healthcare providers and social interaction with friends, family and peers.

Conclusion: This study demonstrates that physical, psychological, and social aspects are key factors driving LC patients' HRQL. Gaining a better understanding of how LC patients perceive their HRQL and how it is affected by their illness and therapy will aid patient-centric decision-making across the drug life cycle, by providing stakeholders (drug developers, regulators, reimbursement bodies, and clinicians) insights about the

treatment and disease aspects of importance to LC patients as well as the unmet needs LC patients may have regarding available treatment modalities. Finally, this study underscores a need for individual treatment decision-making that is considerate of uncertainties among LC patients about their future health state, and ways for improving communication between healthcare providers and patients to do so.

Keywords: patient preferences, lung cancer, health-related quality of life, qualitative research, focus group discussions, patient-reported outcome (PRO), drug development, patient-relevant treatment outcomes

INTRODUCTION

Lung cancer (LC) is the leading cause of cancer mortality due to its high incidence and low survival rate. With 2.09 million new cases and 1.76 million deaths in 2018 worldwide, LC is the deadliest cancer in men and second in women (Bray et al., 2018). *Non-small cell lung cancer* (NSCLC) is the most prevalent type of LC, accounting for 85–90% of all LC cases worldwide (Remon et al., 2020). With the emergence of innovative treatment modalities over the past decade, the LC treatment landscape has changed dramatically, with the range of options now extending beyond well-established therapies such as surgery, radiotherapy, and chemotherapy to include such new regimens such as targeted therapy, immunotherapy, and chemoimmunotherapy (Dong et al., 2019; Remon et al., 2020). LC treatments in development and use today differ in terms of benefits (e.g., in terms of progression-free survival, overall survival, response rate, and long-term benefits), side-effects (e.g., pain, nausea, vomiting, breathing problems, fatigue, physical changes such as weight changes, bleeding, hair loss, and uncertain long-term safety), psychological impact (e.g., emotional distress, affective disorders), route of administration, and treatment schedule (Dong et al., 2019; King-Kallimanis et al., 2019; Van Der Weijst et al., 2019; Remon et al., 2020).

While recent developments have resulted in a greater range of treatment options for NSCLC patients, the variety of LC treatment options and their associated characteristics also raises uncertainty regarding the key treatment and disease aspects affecting LC patients' *health-related quality of life* (HRQL) (Blinman et al., 2010; Maric et al., 2010; Grassi et al., 2017). HRQL has been defined by the *US Food and Drug Administration* (FDA) as *"a multi-domain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of [his/her] life"* (US Food and Drug Administration, 2006). The variety of LC treatments, their characteristics, and the ascendency of patient-centered care require an informed decision-making by stakeholders involved in the medicinal product development, evaluation, and prescription that involves the elicitation and consideration of patient preferences (Marzorati and Pravettoni, 2017). As noted in prior research, patient preferences represent a crucial consideration for both clinical decision-making by healthcare providers, as well as decision-making by pharmaceutical companies, regulators, *Health Technology Assessment* (HTA) bodies, payers, and across the medicinal product life cycle (Petrocchi et al., 2021; The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2020; Janssens et al., 2019a; Janssens et al., 2019b; Soekhai et al., 2019; van Overbeeke et al., 2019a; van Overbeeke et al., 2019b; Whichello et al., 2019).

One way of determining what matters to patients is via performing a patient preference study. Patient preference studies use qualitative and/or quantitative methods to identify which treatment characteristics are important to patients, how important, and which tradeoffs patients are willing to make between various characteristics (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2020; Patient Preference Information–Voluntary Submission, 2016; Patient-Focused Drug Development, 2018). In doing so, such studies illuminate key aspects affecting patients' quality of life. Eliciting preferences from NSCLC patients is especially valuable in view of uncertainties regarding the impact of different (novel) LC treatments' effects on patients' lives, attitudes, and choices towards treatments. In addition, the FDA emphasizes that patient preference information is especially valuable in "preference sensitive situations", i.e., situations where: 1) multiple treatment options exist and there is no option that is clearly superior for all patients, 2) the evidence supporting one option over others is considerably uncertain or variable, and 3) patients' views about the most important benefits and acceptable risks of a technology vary considerably within a population and may differ from those of healthcare professionals (US Food and Drug Administration, 2016). Decision-making regarding the development, market approval, and reimbursement of new NSCLC treatments is therefore a preference sensitive situation, as such decision-making may depend on the preferences of patients for these diverse treatment characteristics (Blinman et al., 2010; Marzorati and Pravettoni, 2017; Petrocchi et al., 2021).

Previous empirical preference studies among LC patients were mostly quantitative in nature and have focused on chemotherapy (Hirose et al., 2005; Hirose et al., 2009; Blinman et al., 2010; Schmidt et al., 2016; Schmidt et al., 2017; Sugitani et al., 2020). This contrasts with the added value that qualitative methods provide; qualitative methods provide in-depth and meaningful information from patients, and hence, their use is recommended for understanding what matters most to patients, and why. Furthermore, qualitative methods with patients reduce the potential for misspecification of aspects most important for patients, for inclusion in drug development and evaluation, and thereby avoid overreliance on the views of experts and researchers (Coast et al., 2012). In doing so, using qualitative research for understanding what matters

most to patients in relation to their HRQL, the data collected on patient perspectives and preferences is likely to be more comprehensive, meaningful, and a valid interpretation of the true patient perspective (47). Therefore, the present qualitative study aimed to investigate how LC patients perceive their HRQL and what LC patients consider to be most important in determining their HRQL, thereby expanding the body of evidence regarding LC patient preferences.

METHODS

Study Context and Design

This study was conducted as part of the *Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle* (PREFER) project. The PREFER project's objective is to develop evidence-based recommendations to inform stakeholders on how to conduct patient preference studies and how their results can be implemented in the drug decision-making process (PREFER, 2020). The present paper presents a secondary data analysis of *focus group discussions* (FGDs) with LC patients. A primary analysis of the discussions, describing overarching themes of treatment features of importance to LC patients has been published elsewhere (Petrocchi et al., 2021), as well as detailed information regarding the applied qualitative methodologies and limitations (Durosini et al., 2021). However, a specific and in-depth analysis of how LC patients perceive their HRQL, and what they consider to be the treatment- and disease-related factors influencing their HRQL was out of scope in the abovementioned papers. Therefore, the present paper provides a further analysis of cross-country HRQL related themes and detailed insights into the opinions from Italian and Belgian patients with stage III and IV NSCLC.

Participant Recruitment

Participants were recruited in Italy and Belgium to allow for an understanding of which treatment aspects influencing HRQL were important for LC patients with differing patient characteristics, backgrounds, and who lived in countries with different kinds of healthcare systems (e.g., in terms of financing, service provision, and access to healthcare). Participants were purposely recruited between September 2019 and October 2019 by the treating oncologists at the Thoracic Oncology Division of the European Institute of Oncology in Milan (Italy) and the Respiratory Oncology Department of the University Hospitals in Leuven (Belgium). In Belgium, the *"Ethische Commissie Onderzoek UZ/KU Leuven"* approved the study (reference S63007). In Italy, the *"Ethical Committee of the European Institute of Oncology IRCCS IEO"* approved the study (reference 1,027/19-IEO 1093).

Inclusion and exclusion criteria for the FGDs were defined and described in the protocol paper (Durosini et al., 2021). In particular, the following inclusion criteria were applied: 1) in treatment patients with a histological or cytological diagnosis of NSCLC stage III or IV as classified by the Union for International Cancer Control TNM Classification of Malignant Tumors (UICC TNM VIII Edition); 2) adult patients (≥18 years old). Stage III or IV patients were eligible for inclusion since they were more likely to have experienced several treatment lines and thus would be able to contribute to a discussion regarding a broader range of treatment modalities and effects. Furthermore, uncertainty among decision-makers (clinicians, patients, regulators, HTA/bodies, and reimbursement agencies) seems to be particularly present in the context of late-stage LC, due to the increasing amount of treatment options and treatment combinations for all stages of NSCLC, but especially for advanced stage LC (US Food and Drug Administration, 2020). Exclusion criteria were: 1) cognitive impairment or inadequate verbal skills that may render them incapable of agreeing to participate in an informed and voluntary fashion (as evaluated by the clinician); 2) inability to understand study materials (as evaluated by the clinician); 3) physical or psychological impairment that prohibits their participation in the focus group (as evaluated by the clinician). The clinical partners of both study centers made a primary selection of patients that could be contacted based on their health status and the inclusion and exclusion criteria. These patients were asked if they were interested in participating either during a visit to the hospital, by phone, or during hospitalization.

Qualitative Approach and Data Collection

The qualitative study design involved four FGDs with between 5-7 LC patients per group (Durosini et al., 2021). FGDs were chosen as a method for data collection because they allow for interactivity between participants, active discussions guided by the researchers, and thereby may generate topics that researchers were previously unaware of (see **Supplementary Appendix S1** for focus group guide and questions) (Durosini et al., 2021). FGDs were conducted by the authors of this paper (SP and SO in Italy and RJ, RA, and IH in Belgium), who have varying backgrounds (psychology, pharmacology, regulatory sciences, drug development) and experience with qualitative approaches and conducting FGDs. All discussions involved Dutch-speaking patients and Italian-speaking patients and were audio-recorded with participants' consent.

Every FGD started with the same procedure; participants were given an information sheet, informed consent form, and a survey containing questions asking about their demographics. After each participant signed the informed consent, a FGD guide containing a series of open questions was followed (**Supplementary Appendix S1**) (Durosini et al., 2021). To increase procedural comparability among the discussions conducted in the two countries, both teams used the same discussion guide. When the moderator judged that the discussion on a specific topic had reached a point of saturation, a predefined list of potential treatment characteristics (Durosini et al., 2021) based on a literature review was read out loud as a way to spark further conversation. When no other new characteristics or insights emerged on a specific topic, the next question was asked. Participants' health literacy was assessed using the Chew Brief Literacy Scale (Chew et al., 2004) and a short questionnaire was completed by the participants to gather information on socio-demographics.

Data Processing and Analysis

The audio-recordings of all FGDs were transcribed ad verbatim in the original language and pseudonymized. Names were replaced by codes, and all other personal information not related to their treatment experience was removed. Transcripts were subsequently translated to English by a professional transcribing company (Lacey and Luff, 2007). Thematic analysis, as described in detail in Durosini et al. (2021), was used to assess the transcripts and notes from the FGDs. Data were analyzed using NVivo software (edition 12). The thematic analysis and focus group conduct used a mixed bottom-up and top-down approach. Specifically, the bottom-up (inductive) approach implied that patients were asked open questions about which aspects matter most to them. A bottom-up analysis was used to derive themes from their answers to these open questions. Conversely, a top-down (deductive) approach was done by asking about, and analyzing patients' views on the side-effects and treatment outcomes associated with marketed and investigational drugs identified in the scoping literature review outlined in Durosini et al. (2021). The deductive analysis also considered the HRQL definition of the FDA to assess which aspects patients felt were important in determining their HRQL and how they could be categorized as physical, psychological, or social aspects. A combined bottom-up and top-down approach was taken in order to ensure the treatment aspects reflected in the themes are those that matter most to patients with respect to their HRQL, and inclusive of those side-effects and treatment outcomes of investigational and marketed drugs identified in the literature review that patients find important. Specifically, a bottom-up approach, i.e., deriving the themes directly via patients was taken to ensure that the themes were key in determining patients' HRQL, plausible from the patients' perspective, i.e., align with their experienced, lived disease and treatment experience. A bottom-up approach thereby helped avoid omitting potentially relevant treatment aspects included in the themes, and thereby avoid potential bias in the findings. In addition, a top down approach was taken as well, to ensure patients provide their views on potential "future" treatment outcomes and side-effects, even though they have not experienced them but could be definitive in determining their HRQL.

RESULTS

Study Population

Belgium

In total, 12 stage III or IV NSCLC patients, contacted by the clinical partner of the university hospital in Leuven (Belgium), agreed to participate in the FGDs. The average response rate across the two FGDs was 56%, meaning that from all contacted patients 56% agreed to participate. Age characteristics were reasonably similar among the two FGDs with a mean age of 64.9 years [SD age: 6.82 years; age range: 52–78 years; 83% males; median age: 66.5 years; inter-quartile age (IQR): 6.8 years]. On average, there was a 2.8-years gap between diagnosis and participation in the FGD (mean age at diagnosis: 62.1 years; age range: 48–73 years). Using Chew's three-item health literacy screening, all patients were coded as 'moderate literacy' (Chew et al., 2004). The majority of LC patients indicated to have as highest education: 1) a high school diploma (41,7%), 2) a bachelor diploma (25,0%), 3) no high school diploma (16,7%), or 4) a master diploma (16,7%). Nine participants (75,0%) reported that they were receiving LC treatment at the time of the FGD, with all patients not receiving treatment (n = 3) being concentrated in the first FGD. The most frequently taken treatments among Belgian participants were immunotherapy (42%), chemotherapy (17%), and a combination of chemotherapy and immunotherapy (8%).

Italy

A total of 12 NSCLC patients stage III or IV agreed to participate in the FGDs in Italy, and the response rate was 57%. Age characteristics were similar among the two FGDs with a mean age of 57.33 years (SD age: 8.56 years; age range: 42–72 years; 42% males; median age: 58.5 years; IQR: 13.5 years). On average, there was a 2.08-years gap between diagnosis and participation in the FGD (mean age at diagnosis: 55.25 years; age range: 41–68 years). Patients were coded as 'moderate literacy'. The majority of LC patients indicated to have a high school diploma (41,6%), whereas 58% declared they did not finish high school. All 12 participants were receiving treatment at the time of the FGD. The most frequently taken treatments among Italian participants were immunotherapy (33%), chemotherapy, (17%), a combination of chemotherapy and immunotherapy (17%), and biological therapy (33%).

Across the four focus groups in Italy and Belgium, participants' median age was 62 years (IQR: 9.3) and the average age was 61 years.

Themes Capturing Key Determinants of Health-Related Quality of Life Among Lung Cancer Patients

Patients agreed on the importance of quality of life. Patients shared several personal definitions of quality of life and what it meant to them. Participants often reflected on quality of life in relation to a personal "endpoint", where the benefits of the treatment would no longer outweigh the burden. For some participants, these endpoints were general: *"It has to be a life worth living."* #FG2_A/Belgium, *"Try to live a life as normal as possible, as similar as possible to before."* #FG1_C/Italy, and *"The expectation was to start getting my life back a bit. Professor XX also told me, "My task is to bring you back to life first."* #FG1_D/Italy. Other participants had a clear description of which side-effects would bear such a decline in quality of life that they would stop undergoing treatment: *"I will undergo every treatment as long as my brain functions."* #FG2_C/Belgium. Patients unmistakably expressed during the FGDs that they wanted to live longer but not at any cost, but how this "cost" was assessed and how big the range of "worth living" was, differed from patient to patient. It was clear though, that across both countries, LC patients' quality of life was influenced by physical, psychological, and social aspects. Based on this, results of the FGDs are presented

below according to the main themes identified through the thematic analysis of the focus group discussions: physical aspects, psychological aspects, and social aspects.

Physical Aspects Influencing Health-Related Quality of Life: Skin Conditions, Nausea, Fatigue, Risk of Infections, Sensory Abnormalities, Pain, and Changes in Physical Appearance

Skin Conditions

Several patients reported an undeniable itching feeling, especially as a side effect of immunotherapy, on diverse parts of their body resulting in the urge to scratch. This itching feeling was persistent, causing patients to continue to scratch their skin until it bled: *"That's a side-effect of the immunotherapy, you start to itch, then I begin to scratch it, but you keep scratching till you get through it.—Till you get through everything, till you bleed."* #FG1_C/Belgium + #FG1_G/Belgium, "*(My) nails were breaking, I was getting cuts. I said to my son "But how can I go on like this?""* #FG1_E/Italy, and "*The other one (pill) really killed me. In the first few months I lost all of the skin from my hands, face, spots."* #FG2_B/Italy. This itching feeling was debilitating for them since this did not allow them to focus on other activities: *"It'd drive you mad, really."* #FG1_G/Belgium, and *"Essentially, the fact that I was losing my skin, my hands were bleeding. . . how can I live like that? Better to die. . ."* #FG2_B/Italy. Other patients also had some skin conditions like a rash or burns from chemotherapy or radiation therapy, which together with the bleeding/peeling skin negatively affected patients body image (as further described in "Changes in Physical Appearance").

Nausea

The theme of nausea emerged in both countries and was experienced by the majority of participants. Nausea and also vomiting in some cases were highly related to chemotherapy: *"what you experience with chemo, the nausea."* #FG2_C/Belgium, *"a sense of nausea. . . iron, it was like I had iron inside me, rust."* #FG2_B/Italy, and *"I couldn't even manage to take (name of the drug), the side effect was fainting, or almost. It was continuing and continuing vomiting and nothing ever came up because I wasn't able to hydrate myself."* #FG1_B/Italy. Nausea had a significant effect on the participants' possibility to live a qualitative life because, firstly, they could sometimes no longer engage in some activities because of the nauseous feelings: *"I had nausea and you're a different person."* #FG2_A/Belgium and the nausea could not be helped by any medication: *"I was in bed and I remained weak. Then at a certain point they took me to the emergency room, I spent a night there, because I could not manage to take things (medication) to normalize the situation."* #FG1_B/Italy, and *"Chemo is devastating. . . it kills you. . . you are dead, for 4 months it is like being dead."* #FG2B/Italy. Secondly, the feeling was a constant reminder of their cancer. *"Yes, you have a lot of side effects, such as nausea, that remind you of it."* #FG1_A/Belgium. In addition, nausea impedes patients to have a normal family life: "*When I need to prepare food I feel sick. When I need to start preparing a meal for my husband and my daughter, not only am I not hungry but it actually disgusts me."* #FG1_E/Italy. Another patient even needed to quit his therapy because of nausea: *"They brought me to the emergency room because I could not eat any more, I vomited twenty times, after two times (receiving chemotherapy), I had to stop it because it was highly toxic. . ."* #FG1_B/Italy. One patient explained that he had experienced chemotherapy more than 30 years ago and voiced that he felt that the management of nausea related to chemotherapy had already improved significantly over the years: "*Yes, the medication has improved, yes. There's no doubt about it. Compared with before, I got chemo then for an entire year. There wasn't much to smile about. (. . .) at the moment itself you had to throw up, there wasn't enough medicine at the time to prevent it."* #FG2_B/Belgium.

Fatigue

Immunotherapy and chemotherapy were two treatment modalities that were reported to cause fatigue, so intense and exhausting that it hampered patients in performing any physical and psychological activities: "*Yesterday I was watching Grenslanders with my children, I saw the first 10 minutes and then I was out."* #FG2_A/Belgium, and *"With chemo I was so tired, (. . .), I have always walked, I have climbed so many stairs and steps in my life and, conversely, since I have had chemo, I have found it difficult to walk, to cook, I was making junk food, my poor husband who was used to eating well. . . I wasn't able to make more than that (. . .) I would say to these people who make these drugs to try to cut that out because otherwise your quality of life is impacted."* #FG1_F/Italy. When the subject of fatigue came up, it was noticeable that everyone had a story to tell. The fact that everyone could recognize this particular side effect and that they were not the only one going through this made them feel better: *"I'm soooo tired. I could sleep all day long, and I'm happy because she's got that too."* #FG1_G/Belgium. The expectations of patients concerning their physical activity varied, ranging from *"I might just lie down for half an hour and I'll be right as rain. But after two or 3 hours I'm shattered again."* #FG1_G/Belgium to *"I get tired earlier, but I can easily go walking for half a day, Nordic walking but I'm really tired afterwards."* #FG1_D/Belgium.

Risk of Infections

Lower immunity was mostly discussed in terms of the risk of getting an infection. Lower immunity was seen as being detrimental in two ways. First, it increased patients' likelihood of getting infections: *"I also got two infections in my big toe, for which the doctor had actually sent me to the cosmetologist, they had to suspend use of the drug for 2 weeks because there was this infection in this big toe and then it got better and there was nothing more."* #FG1_E/Italy. Second, it prevented patients from participating in some activities, thus limiting their freedom: *"I can still remember when my grandson had just learned to walk, he came over to me and they all said 'no don't, don't, you have a cold, you have to stay away'."* #FG2_D/Belgium, and "*Your immune system is at its lowest now. Don't stand near sick people in the shop,*

stay away from the bakery, because if there's someone there who has something, you'll get it too." #FG1_B/Belgium.

Sensory Abnormalities

The theme of sensory abnormalities relates to a multitude of side effects including: taste differences, tingling, hearing impairment, and different perception of temperature. Firstly, taste differences were observed both in food as in drinks and were associated with chemotherapy: *"I enjoy drinking coke, and I couldn't drink coke anymore because the only thing I could still taste in the cola was the citric acid."* #FG1_C/Belgium, *"The flavour of food too."* #FG1_A/Belgium, *"I don't have the pleasure of food."* FG2_C/Italy. Secondly, tingling was another side effect, which was the result of nerve damage caused by radiation or chemotherapy. The participants that experienced this were all annoyed by it but were able to put it aside for the greater goal: *"My feet tingle because the nerves are dying because of the chemo. It's really annoying, but you learn to live with it don't you."* #FG1_B/Belgium. Thirdly, one patient was faced with hearing loss as a result of his treatment. The possibility of no longer being able to hear was too much for him. Other participants were also convinced that they would stop the treatment if it would make them lose their hearing: *"But that was the choice, did I want to go deaf or did I want—well yes, that wasn't an option for me."* #FG1_F/Belgium.

Pain

Pain, both due to the cancer and the therapy, was another category of issues that was found to negatively influence quality of life. Participants extensively discussed pain caused by the therapy: *"No, no, I was crying every night but not because of the cancer, because of the pain."* #FG1_D/Italy. Other patients described pain as due to the metastasis of the cancer. One participant for example described severe headaches due to the brain metastases: *"I get headaches and I can't take anything for it. (. . .) I can eat them like candy."* #FG1_C/Belgium. One participant with several metastases with one being bone metastases went through a lot of pain: *"Bone pain is something else, that's very intense pain."* #FG2_C/Belgium. This patient stressed the fact that some cancers cause pain that even the most potent painkillers cannot alleviate. This pain was so intense that one could become dependent on pain medication: *"Pain medication (. . .) in the room um, X percent of the patients couldn't wait their turn anymore and were really almost aggressive, hysterical, because of the pain."* #FG2_C/Belgium. The majority of the participants noted, however, that they had not experienced such severe pain. Nonetheless, they were all convinced that they were a select group since they had met several patients over the years who had encountered excruciating pain. Notwithstanding, some patients suggested that they would bear pain in exchange for seeing the cancer stop growing: *"I would accept being bed-bound, having nausea, pain in my legs, and maybe I would also accept that I may not completely recover, if I were sure that it (the cancer) would stop growing."* #FG1_C/Italy, and *"In any case the moral of the story is that today I would do everything that I have done again, despite all the pain."* #FG2_B/Italy.

Changes in Physical Appearance

Patients highlighted that bodily changes, caused both by the cancer and LC therapies, made them insecure about their body image, and also negatively impacted how they interacted with others (as further described in "Social Interaction"). Specifically, patients stated that excessive changes to their body weight would reinforce and publicly make the idea of being an ill person: *"Yes, excessive changes to the body are always linked to the issue of quality of life. The fact that. . . it is as if I don't want others to see that I am unwell because it is also a way for me to be stronger. If other people treat me like a normal person, pass time with me, I feel stronger."* #FG1_A/Italy, and *"I am not eating much and I get angry because in other people's eyes it looks like I am eating whole roast chickens myself, and yet that's how it is. . . I put on all these kilograms and I do not know why."* FG1_E/Italy. Weight gain is also an issue because sometimes people around patients seem to blame him/her: *"My sister tells me 'But look how swollen you are.' But what can I say? She thinks I eat a lot, but I don't."* #FG_B/Italy. Hair loss, particularly associated with chemotherapy, seemed to be a side effect that did not bother all patients in the same way. Whether or not hair loss was acceptable seemed to depend on the severity of their hair loss. Whereas for some the experienced hair loss was acceptable: *"The hair (loss) is alright, it's nothing."* #FG1_C/Italy, the idea of losing all hair, would be: *"Devastating on the personal level."* #FG1_B/Italy for other patients. Other participants did not experience hair loss as a side-effect of their NSCLC chemotherapy.

Psychological Aspects Influencing Health-Related Quality of Life: Autonomy, Freedom and Independence, and Uncertainties Regarding Patients' Future Health State

Patients were very vocal on the psychological effects of cancer. Most of the patients actively sought for the positive aspects and tried to remain hopeful for the future, portraying a "fighter's mentality": *"You have to go, keep working, you have to keep morale up."* #FG1_C/Belgium, *"I'm only going to go crawl into a corner, sit and cry, when the professor comes and says: we don't have anything else for you anymore. Then you still have time to mourn."* #FG2_A/Belgium, and *"I react and make efforts (. . .) in any case your life changes in a moment. (. . .) you need to change your lifestyle, you need to change and reset everything a bit, and gradually you get used to it. . . I am doing quite well now."* FG2_A/Italy. In general, participants receiving immunotherapy at the time of the FGDs seemed quite happy with their health status. One of the things that was not always put into words but became visible, was the pleasure they felt when others related to their story. Knowing others were going through the same process and face the same negative aspects created a connection between patients: *"You get to know the other people, you get more sociable, you share your problems with one another. . ."* #FG1_G/Belgium. Several patients showed interest in connecting through patient organizations with people who had had similar experiences.

Autonomy, Freedom, and Independence

While someone found it important to *"still go on holiday"* #FG1_F/Belgium, others found meaning in *"going back to work"* #FG1_G/Belgium or *"riding my bike"* and *"going to the vegetable garden"* #FG2_B/Italy. Someone else emphasized the need to go back to a normal life like before having cancer and receiving therapy at the hospital: *"I had radiotherapy, five applications and then finally I said I'm going on holiday for a while."* #FG1_F/Italy. Sometimes patients chafed at the realization that they were less independent and free as before: *"I find it really difficult to get out of it. My sister comes, she takes me out, but I don't want to go out, I don't want to see people and this is a terrible lifestyle for someone who has this type of disease. My daughter's father in law calls me and tells me 'Come here so we can chat' and I don't want to chat, 'come here so we can go out, let's go out for a walk' and I don't want to walk."* #FG1_E/Italy because the treatment regimen deprives them of their independence: *"If I need to take a drug every 15 minutes, how can I manage my daily life?"* #FG1_E/Italy.

Several patients stressed the importance of being able to be professionally active. One patient found great joy but also meaning in her work, and by losing her work, she found that she had lost a big part of her life: *"Sitting about at home isn't easy if you've always worked. I mean it's really driving me mad."* #FG1_G/Belgium. On the other hand, someone else complained about the duality between still having all his duties but being deprived of the things he enjoyed: *"I'm still well enough to go working and to do whatever else, but there are two things that I can't do. One is that I can't drive my own car, and the other is that I can't fly. So, I can't go on holiday."* #FG1_C/Belgium. This restriction on personal freedom, including not being able to drive a car, emerged as an important factor, one mentioned by every participant: *"You're not allowed to drive anymore? I'd hate that.—Yes, it's a restriction, not a bodily restriction but it's…"* #FG1_F/Belgium + #FG1_B/Belgium. This was mentioned to be linked to staying socially active; being homebound limited their ability to connect with others and to maintain social interactions. Patients further stated that being confined to bed, as a result of a therapy, with a consequent loss of independence and autonomy could be one of the most problematic side effects of a therapy. Further, while they considered it acceptable to be in need of *"perhaps a little help"* and, for a limited time, they clearly *"would prefer to be independent"* #FG1_B/Italy and feared being bed-bound for an indefinite period of time.

Uncertainty Regarding Their Future Health State

As participants were all in an advanced stage of LC, they were aware of the fact that LC may very likely be deadly for them, and this faced them with the constant fear of how much longer they had to live. On several occasions, they reflected on the fact that this created a situation with a lot of uncertainty for patients and their relatives. They recognized that the path might be long: *"you don't recover straight away… it takes a bit of time, it takes some years, at least that is the case for the experiences that I have encountered up until now."* FG2_A/Italy. They often feel uncertainty related to the time they had to live: *"I think that what I wanted to know was to try to understand how long I had left to live, nobody told me that… alright, there must be rules, you can go on for between one and five (years), or you will die a natural death."* #FG2_B/Italy. In addition, the uncertainty whether their health status will stay the same for a more extended period of time made it hard for patients to engage in long term projects: *"Long term there's not much anymore."* #FG1_B/Belgium, *"I live day by day. Every day is gold for me."* FG1_C/Italy. Many of the participants believed that the moment of diagnosis, one's long-term plans drifted away and were replaced by thoughts of one's funeral and estate planning. This causes a difficult situation for both the patient and his/her partner since they can no longer plan ahead anymore. Also, the question of whether the medication will continue to work, whether they will still be able to get the medicine after their study ended, raised concerns among participants: *"It's so new and long term, will it keep working, will it stop?"* #FG1_F/Belgium and *"What do I expect if this does not work? Well… I am becoming a grandmother and I need to know if I will see my grandchild next year!"* #FG1_B/Italy. These questions created uncertainty resulting in patients suffering and worrying: *"Everything's always maybe, maybe, maybe."* #FG1_E/Belgium. At a beginning of a care path, some patients express their feelings of being invincible: *"This genetic mutation, here at the hospital they immediately gave me this drug and, at the start, I felt strong with this drug, for me it was also a positive way to react, I immediately had the impression that this drug was working very well."* #FG1_C/Italy, whereas these feelings decline when the therapy does not work anymore or in case of relapse: *"Yes, that's right, day by day it is OK, but I am a little more negative than before because before I had a bit more hope and, seeing that it is not going well one moment I am quite… I had surgery 2 years ago, not even one and a half years, it relapsed."* #FG1_B/Italy. One of the things patients perceived as a kind of certainty and peace of mind was the knowledge that if the current treatment option would fail, other treatment options were still available: *"If there's a setback, we still have !ve or six other options."* #FG1_G/Belgium. Others who did not know whether other medication would become available faced much more uncertainty: *"You're sitting on the joyride that is science, and you just have to hope it'll keep moving."* #FG2_A/Belgium.

Those patients who were satisfied with his or her health status at the time of the FGD did not want to receive negative news that might disturb their delicate psychological equilibrium. Every patient had to go to the scanner every once in a while. This moment was generally marked as a moment of considerable uncertainty. The scanner gave them an update on how they were doing and could possibly drastically affect their lives: *"I had to wait 5 months for the results of a scan. That's too long for me. (…) there's too much uncertainty."* #FG1_G/Belgium, *"I have a CT scan in 1 week. For me, that is the most tragic moment because I live with incredible anxiety."* #FG1_C/Italy, *"At the start you needed to have a scan every 2 months. Now it's every 3 months, but you still feel tense, you know."* #FG2_B/Belgium. Multiple patients noted that besides for them, this was also a heavy psychological burden on their partner and other relatives:

"Then my wife will say—well, she'll start worrying. Especially because my scan date is getting closer." #FG2_D/Belgium.

Social Aspects Influencing Health-Related Quality of Life: Social Interaction and Communication With Healthcare Providers

Social Interaction

Patients identified their personal situation as an important factor influencing their attitude, behavior, and assessments towards treatment options and compliance. In particular, family composition affected nearly all participants; the presence of a partner, children, grandchildren, gave participants a reason to live and fight: *"I thought, I'll never see the little man grow up. He'll be six in December. That's a gift that I've been given and that I'm very grateful for."* #FG2_D/Belgium, *"I am becoming a grandmother and I need to know if I will see my grandchild next year."* #FG1_B/Italy, and *"I have a daughter now, who still lives with us, the other daughters are married, grandchildren, I am starting to collect them from school again."* #FG2_D/Italy. On the other hand, some patients considered family to be a reason to stop treatment. Two participants said they would rather stop treatment and terminate their life than to put their family through a lot of suffering. The first participant watched her mom deteriorate and did not want her children to remember her that way: *"I watched her waste away and I said: 'No, I don't want to put my children through that."* #FG1_G/Belgium. The second participant applied a more general principle; he did not want his relatives to perceive him as a burden: *"As long as I'm not a burden to someone else then yes, I'll go through with it."* #FG2_E/Belgium.

Although patients described interacting in social activities as one of the favorable aspects, the effects of cancer and treatment can hinder their ability to participate. Several patients reported that they did not feel comfortable going outside and meeting people because of their altered looks. Hair loss and weight fluctuations (see also 'Changes in Physical Appearance') were the two changes participants named as having the most significant effect on how they felt about themselves and how people perceived them: "*I lost my hair, I lost 12 kilos, I had a huge moustache, that's gone (. . .) you know what it's like, they say 'hey hello' and then 'oh did you see him? He really didn't look well did he?"* #FG1_A/Belgium and "*Perhaps I should not go out. . . when I go out, I do not go out to gain people's compassion, because I hate the "Poor thing. . .", I need to go out with a smile because if not they will say "Look how pale she is", look how she is, look. . ."* #FG1_B/Italy. The idea they would have to face the gossip and the confrontation with others scared them. On the other hand, participants who did not have any visual side effects criticized that they weren't seen as a cancer patient and were subsequently not recognized as "having a hard time"'. The fact that people did not see it made them feel their illness was not as valid as someone with visible symptoms or side effects. Another participant felt he should keep his cancer a secret to people around them, since telling them would be detrimental for their social interactions. When people know you have cancer, they become scared to visit you or to say something wrong: *"I hide it, the fact I have cancer. (. . .) Because if you tell them, people don't know what to say to you."* #FG1_B/Belgium. In conclusion, all participants agreed they wanted their social interactions to remain as much as possible unchanged despite their cancer.

Communication With Healthcare Providers

Patients spoke about the positive and negative moments of communication with healthcare workers. The most prominent negative feedback patients gave was that they felt the hospital was too big, which made it difficult to have a good flow of information.—*"The hospital is far too big. That there isn't enough interaction."* #FG2_A/Belgium, and *"The hospital really is like a factory."* #FG2_C/Belgium. Because the hospital is too big, patients had to repeat their concerns and problems several times before action was taken. Participants attributed this lack of responsiveness to the fact that the high number of different staff (both referring to different types of healthcare professionals and a high turnover in the hospital staff) hampered efficient communication between healthcare workers and patients: *"I showed my edema to one of the people running the study here and yes she said: 'that could be one of the consequences and that can be burdensome'. But there was no reaction to try and work on it anymore until I saw XXX again, "Yes" she said, 'Why didn't you come down here to the edema department?"* #FG2_A/Belgium. The most vocal participants noted that the way you got treated depended highly on the assertiveness of the patient. Surprisingly, patients involved in a clinical trial reported experiencing better communication, although these patients also went to the same hospital. However, when the study ended, they encountered the same experiences as the patients not involved in a clinical trial: *"The only thing I think is a pity about it (the clinical trial) is (. . .) after the study was finished. Then you are kind of abandoned, left to your fate."* #FG1_G/Belgium. Despite the limited flow of information, patients stressed the fact that healthcare workers were always friendly and that their motivation and how they interacted with patients sparked joy in difficult times.

The opinions on the exchange and availability of information were highly divided. One patient felt that *"physicians don't like giving bad news"* #FG1_B/Belgium although he would rather get all possible information to prepare himself. Another patient, however, did not share the same experience: *"They explained properly to me what the effects would be and how long it would last."* #FG1_E/Belgium. One patient, however, noted that he believed that receiving too much information was burdensome, and he would rather not know. The information was often too technical and not interpretable by a layman: *"You don't understand what you are looking at if you saw your blood results. Just lots of figures."* #FG1_F/Belgium. About half of the participants were eager to receive additional information on how to live with LC and LC itself. They requested they would be updated on new clinical possibilities and potential future treatments: *"I'm curious about the new medication you know. But yes, we're going to have to wait."* #FG1_A/Belgium. They felt that the available information was too limited, and their attempts to gain knowledge were discouraged by doctors: *"As soon as you start talking about for*

example cannabis oil here in the University Hospital, they say sorry, that's not what we do." #FG2_D/Belgium.

Participants spoke about delivering terrible news to patients in a manner considered inappropriate by themselves: *"How long will I need to take this pill?", and he (the doctor) told me "Ah, madam, for your entire life!"* #FG1_E/Italy and *"in my ignorance I said: 'But can't I continue the immunotherapy?' And he (the doctor) looked at me and said 'Madam, do you want to die?' But he said it in a provocative manner and I remained quiet"* #FG1_F/Italy. A participant received bad news on the phone: *"They called me to tell me on the phone that they'd operate on my head. Like that, on the phone."* #FG1_C/Belgium. He regretted this since after this call he had had many questions and couldn't sleep because of the stress it caused him. Another participant did not receive bad news himself but remarked based on his experience observing other people receiving bad news: *"As an outpatient, you're all in that circle, in the circles. Then they close the curtain and the professor comes and tells you some bad news!"* #FG2_A/Belgium. Not only would he not appreciate receiving bad news this way himself. Seeing and hearing others who have the same cancer receive bad news causes emotional distress to the surrounding patients as well.

DISCUSSION

This study reveals in-depth insights into how LC patients perceive their HRQL and the factors that are most impactful in determining their HRQL. In particular, LC patients prioritized aspects related to physical, psychological, and social aspects influencing HRQL. Within the category of physical aspects, patients highlighted the following symptoms and side-effects: skin conditions, nausea, fatigue, risk of infection, sensory abnormalities, pain, and changes in physical appearance. Among the psychological aspects, patients discussed autonomy, freedom and independence, and uncertainties regarding their future health state. Finally, patients highlighted the importance of social interaction and communication with healthcare providers related to the theme of social aspects.

Gaining a better understanding of how LC patients perceive the ways their HRQL is affected by their illness and therapy may aid patient-centric decision-making across the drug life cycle, by providing stakeholders (drug developers, regulators, reimbursement bodies, and clinicians) insights about the treatment aspects of importance to LC patients as well as the unmet needs LC patients may have regarding available treatments. In particular, aspects of importance to patients identified in this study may inform drug developers about unmet treatment needs not resolved by all available therapies; findings from this study may trigger pharmaceutical companies to develop treatments aiming to avoid or resolve skin conditions, nausea, fatigue, risk of infections, sensory abnormalities, and pain. Of note, treatments for some of these side-effects already exist. For example, while patients considered nausea a disabling side-effect, medications for nausea already exist and are being prescribed, such as Netupitant Palonosetron for the cisplatin/carboplatin schemes on the day of treatment and Alizapride Hydrochloride to be taken at home. Efforts towards a better management of reported problems are also increasing. In the individual treatment context, patients may be encouraged to communicate about their problems and ask healthcare providers (such as their treating oncologist, nurses, oncocoaches) for personal advice for the management of these problems.

However, while acknowledging the existence of treatments for some of the reported issues, for other issues reported by patients, such as fatigue and excruciating pain, our results indicate that presently no treatments are available. Likewise, while recognizing increasing efforts towards improved management and communication of patients' experienced physical and psychosocial side-effects and symptoms, our results highlight that patients in clinical practice are still confronted with both physical and psychosocial issues that require further support. Hence, results from this study argue in favor of a continued and expanded consideration of patients' reported side-effects and symptoms in order to improve LC patients' quality of life. If patients are given the opportunity to ask for help and advice, symptoms and side-effects are likely better managed. Examples of efforts that should be continued and expanded, based on patients' individual needs, include the systematic incorporation of staff trained to support patients from a psychosocial viewpoint (such as psychologists, oncocoaches, social workers), and the expanded use of tools (such as a symptom diary) that assesses patients' physical and psychological burden related to LC and gives healthcare professionals the opportunity to manage the patients' reported problems.

This study also underscores the importance of increasing communication, awareness, and consideration related to the psychological problems of LC patients. Specifically, several patients highlighted during the discussions uncertainties about their future health state. This is likely due to the difficulty healthcare professionals encounter in giving a correct individual prognosis, as it depends on several patient characteristics such as symptom burden and treatment compliance. Patients experiencing uncertainties will likely benefit from the development of solutions to help relieve their uncertainties, such as ways to improve communication towards these patients about the long-term expectations regarding treatment outcomes. For example, based on patients' individual information needs, ways to improve communication with such patients about their long-term treatment results and side-effects, and methodologies supporting clinicians and patients, such as shared decision-making tools, could help address these patients' uncertainties in the individual treatment decision-making context. Patients who are informed about the side effects they may experience in the future will likely be more therapy compliant and this may in turn positively impact their life expectancy. Another solution to support LC patients from a psychosocial viewpoint, that does not require additional time from healthcare providers, may be (online) LC support communities; based on qualitative interviews with advanced LC patients, Walsh and Al Achkar (2021) explore the value of online LC support communities to provide support, camaraderie, and specialized health information.

The importance of capturing and including HRQL data in LC drug development and treatment decision-making has been highlighted by several previous empirical and literature studies. Particularly, the categories identified in the present

study related to physical, emotional, and social impact on HRQL were also revealed in a qualitative interview study by Rowland et al. (2016). Regarding psychological aspects, He et al. (2019) examined the role of LC patients' mood in influencing their HRQL and concluded that interventions that facilitate adaptive coping, reduce negative mood, and enhance positive mood could help to improve or maintain HRQL in patients with advanced LC. Further, Franceschini et al. (2020) retrospective observational cohort study among stage IV LC patients highlight the negative impact of weight changes. Schmidt et al. (2016) conducted a systematic review on LC preference studies and revealed the negative impact of nausea and vomiting on patients HRQL. Likewise, the importance of psychological support and management of uncertainties among LC patients is highlighted by Kurita et al. (2013); suggesting that both during and after treatment, individuals with LC may experience a difficult disease course with higher levels of distress related to physical symptoms, greater challenges in psychological health and daily living, and higher levels of burden from their symptoms than those with other types of cancer.

The physical and psychological aspects influencing HRQL identified in this study may also inform future clinical trial design in LC. Specifically, the identification of clinical trial endpoints as well as the further development of existing patient-reported outcome measures could be broadened to include the physical and psychological side-effects and symptoms of importance to patients highlighted by LC patients in the present study. Several studies have investigated the impact of (novel) NSCLC treatments on HRQL. HallSinghal et al. (2019) performed a systematic review to examine *Patient reported outcomes* (PROs) and HRQL among cancer patients receiving immunotherapies and revealed that few randomized studies reported PROs and patient HRQL data. They also conclude that currently used instruments likely fail to capture important aspects unique to such novel therapies (such as psychosocial aspects related to the disease and treatment) and underscore a need for PROs that are inclusive of these aspects. Likewise, King-Kallimanis et al. 2019 investigated PROs in clinical trials of anti-PD-1/PD-L1 inhibitor immunotherapy, which was a trial submitted to FDA, and conclude that the PRO data collected did not consistently assess important symptomatic events. Bennett et al. (2017) performed systematic review to explore the impact of SCLC on HRQL and the PROs used to capture this impact and conclude that paucity exists regarding the reporting on NSCLC HRQL outcomes. Likewise, Van Der Weijst et al. (2019) performed a systematic literature review of clinical trials in NSCLC and conclude that while reporting HRQL data is important to support clinical decision-making as well as marketing authorisation and reimbursement decisions, the methodology of reporting HRQL remains poor. Among the instruments currently available to measure quality of life, primarily the EORTC QLQ-C30-LC13 (EORTC, 2018), but also the Functional Assessment of Cancer Therapy-Lung (FACT-L) Scale (FACIT, 1995) and its LC specific subscale FACT-LCS (FACT-LCS, 1995) are the most commonly used instruments in LC clinical trials (HallSinghal et al., 2019; King-Kallimanis et al., 2019; Van Der Weijst et al., 2019). Comparing our results to current LC specific scales (EORTC QLQ-C30-LC13 and FACT) reveals that the following side-effects and symptoms, observed in our study, are not included in all presently used HRQL specific LC scales: 1) skin conditions, 2) risk of infections, 3) sensory abnormalities, 4) increased weight, 5) autonomy/independence, 6) uncertainties regarding side-effects and (duration of) positive treatment outcomes, and 7) communication with healthcare providers. The identification of these aspects, such as psychosocial impact of the latest cancer therapies, skin conditions, increased risk of infections, and sensory abnormalities is likely due to the fact that patients participating in the discussions were taking novel treatments (immunotherapies) with novel associated side-effects and uncertainties.

Aligning with conclusions yielded by previous researchers (Bennett et al., 2017; Bouazza et al., 2017; HallSinghal et al., 2019; King-Kallimanis et al., 2019; Van Der Weijst et al., 2019), our findings also argue in favor of systematically including and reporting HRQL instruments and outcomes in LC drug development, regulatory decisions, and clinical shared decision-making to assess and understand the experience of LC patients. Our findings also argue in favor of broadening and updating current HRQL instruments to be inclusive of NSCLC symptomatology and side-effects related to novel (immune) therapies. Further, whereas HRQL scales investigate patients' *quantified* experience with these HRQL aspects, the present study also reveals the added value of incorporating *qualitative* research with patients to understand why these HRQL aspects are important in influencing patients' HRQL and how they specifically impact patients' lives.

This study demonstrates the value of qualitative research with patients as treatment end-users to understand their experience with their illness and treatments. The use of FGDs with open questions enabled to be as inclusive as possible by obtaining both broad and in-depth information on LC patient preferences. Moreover, it allowed seeking answers and clarification to sensitive questions without overburdening patients. Further, interaction between participants with varying treatment and disease exposure ensured a range of symptoms and side-effects across different therapies were revealed, thereby identifying HRQL factors important for patients along the LC spectrum, inclusive of aspects related to varying treatment and disease experiences. Finally, several researchers with varying backgrounds (psychology, drug development, clinical background) were involved in the conduct, analysis, and interpretation of the discussions, ensuring a relevant and correct interpretation of the data. This further allowed us to interpret the data accurately and avoid personal bias.

As for the limitations, it is important to note that the results of this (and other qualitative research) are dependent on the specific time, (individual) drug therapy context, as well as the type of participants included. Therefore, the results need to be interpreted considering the specific time period and context the study took place as well as in view of the type of participants that took part. Patients had to be physically and mentally able to participate in the discussion, and hence, it remains unknown whether patients that were not physically or mentally able to participate would have raised additional aspects in relation to their HRQL. However, even though we did not

include patients physically unable to participate, the study results reveal the detrimental impact of being homebound, and limitations in LC patients' autonomy and independence. Likewise, the importance of psychological aspects influencing HRQL was captured, even though participants who were mentally unable to participate were not included in the discussions. It is also important to note the influence of the individual drug therapy experience of participants on the identified symptoms and side-effects. In the results, we did not differentiate the results according to drug therapy as the goal was to provide an overarching view of important themes to patients across therapies and how they relate to their HRQL. However, it is worth noting that the identified side-effects are often specifically linked to certain therapies. Hence, different treatments (e.g., immuno-vs chemotherapy) will likely differently impact patients' HRQL. For example, while novel immunotherapies are likely linked to fatigue, skin conditions, sensory abnormalities, and psychological uncertainties among patients, chemotherapy is likely linked to nausea, and changes in physical appearance. Another limitation relates to the presence of more dominant speakers in the discussions who went off-topic by telling detailed personal stories and thereby reduced the opportunity for other participants to contribute to the discussion. This was however minimized by the intervention of the discussion moderator experienced in the conduct of FGDs, who was able to involve also more shy participants and engage them in the discussion. Finally, qualitative research with social interactions is researcher-dependent and this likely influenced the narrative of the discussion. This was however counteracted by the involvement of multiple researchers in the conduct and analysis of the discussions. Furthermore, researchers across Italy and Belgium used the same focus group guideline to structure the discussion and ensure the same questions were addressed in each discussion.

CONCLUSION

This study demonstrates that all aspects of HRQL are salient concerns for LC patients in stage III and IV, including physical, psychological, and social aspects. A better understanding of how LC patients perceive their HRQL and how it might be affected by different LC therapies should inform drug developers, regulators, reimbursement bodies, and clinicians about the treatment and disease aspects of importance to LC patients as well as the unmet needs LC patients may have regarding available treatments. Future efforts across stakeholders are needed to translate and incorporate these findings into the development, approval, and reimbursement of drugs that are successful in addressing the symptoms and side-effects that are detrimental to patients' quality of life. Finally, this study underscores a need for individual treatment decision-making that is considerate of uncertainties among LC patients about their future health state, and ways for improving communication between healthcare providers and patients to do so.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they contain information that could compromise interviewees' privacy and consent. Further inquiries should be directed to rosanne.janssens@kuleuven.be.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the European Institute of Oncology IRCCS (IEO, Milan, Italy; reference R1142/20-IEO 1206) and the Ethische Commissie Onderzoek UZ/KU Leuven (Belgium; reference S64022). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors provided substantial input in the study, including in the development of the focus group guidelines, the participant recruitment and data collection, the analysis of results and interpretation. RJ, RA, ES, SP, CC, GO, and GP drafted the manuscript. All the authors have read and approved the final manuscript.

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REFERENCES

Bennett, B. M., Wells, J. R., Panter, C., Yuan, Y., and Penrod, J. R. (2017). The Humanistic Burden of Small Cell Lung Cancer (SCLC): A Systematic Review of Health-Related Quality of Life (HRQoL) Literature. *Front. Pharmacol.* 8, 339. doi:10.3389/fphar.2017.00339

Blinman, P., Alam, M., Duric, V., McLachlan, S. A., and Stockler, M. R. (2010). Patients' Preferences for Chemotherapy in Non-small-cell Lung Cancer: a Systematic Review. *Lung Cancer* 69 (2), 141–147. doi:10.1016/j.lungcan.2010.05.001

Bouazza, Y. B., Chiairi, I., El Kharbouchi, O., De Backer, L., Vanhoutte, G., Janssens, A., et al. (2017). Patient-reported Outcome Measures (PROMs) in the Management of Lung Cancer: A Systematic Review. *Lung Cancer* 113, 140–151. doi:10.1016/j.lungcan.2017.09.011

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., and Jemal, A. (2018). Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* 68 (6), 394–424. doi:10.3322/caac.21492

Chew, L. D., Bradley, K. A., and Boyko, E. J. (2004). Brief Questions to Identify Patients with Inadequate Health Literacy. *Fam. Med.* 36 (8), 588–594.

Coast, J., Al-Janabi, H., Sutton, E. J., Horrocks, S. A., Vosper, A. J., Swancutt, D. R., et al. (2012). Using Qualitative Methods for Attribute Development for Discrete Choice Experiments: Issues and Recommendations. *Health Econ.* 21 (6), 730–741. doi:10.1002/hec.1739

Dong, J., Li, B., Lin, D., Zhou, Q., and Huang, D. (2019). Advances in Targeted Therapy and Immunotherapy for Non-small Cell Lung Cancer Based on Accurate Molecular Typing. *Front. Pharmacol.* 10 (230), 230. doi:10.3389/fphar.2019.00230

Durosini, I., Janssens, R., Arnou, R., Veldwijk, J., Smith, M. Y., Monzani, D., et al. (2021). Patient Preferences for Lung Cancer Treatment: A Qualitative Study Protocol Among Advanced Lung Cancer Patients. *Front. Public Health* 9 (27), 622154. doi:10.3389/fpubh.2021.622154

EORTC (2018). EORTC QLQ-C30-LC13. Available from: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-LC13-English.pdf.

FACIT (1995). Functional Assessment of Cancer Therapy-Lung (FACT-L) Scale. Available from: https://www.facit.org/license-registration-form.

Fact-Lcs (1995). FACT-LCS. Available from: https://www.facit.org/measures/FACT-LCS.

Franceschini, J. P., Jamnik, S., and Santoro, I. L. (2020). Role that Anorexia and Weight Loss Play in Patients with Stage IV Lung Cancer. *J. Bras Pneumol* 46 (4), e20190420. doi:10.36416/1806-3756/e20190420

Grassi, L., Spiegel, D., and Riba, M. (2017). Advancing Psychosocial Care in Cancer Patients. *F1000Res* 6, 2083. doi:10.12688/f1000research.11902.1

HallSinghal, E. T., Singhal, S., Dickerson, J., Gabster, B., Wong, H. N., Aslakson, R. A., et al. (2019). Patient-Reported Outcomes for Cancer Patients Receiving Checkpoint Inhibitors: Opportunities for Palliative Care-A Systematic Review. *J. Pain Symptom Manage.* 58 (1), 137–e1. doi:10.1016/j.jpainsymman.2019.03.015

He, Y., Jian, H., Yan, M., Zhu, J., Li, G., Lou, V. W. Q., et al. (2019). Coping, Mood and Health-Related Quality of Life: a Cross-Sectional Study in Chinese Patients with Advanced Lung Cancer. *BMJ Open* 9 (5), e023672. doi:10.1136/bmjopen-2018-023672

Hirose, T., Horichi, N., Ohmori, T., Kusumoto, S., Sugiyama, T., Shirai, T., et al. (2005). Patients Preferences in Chemotherapy for Advanced Non-small-cell Lung Cancer. *Intern. Med.* 44 (2), 107–113. doi:10.2169/internalmedicine.44.107

Hirose, T., Yamaoka, T., Ohnishi, T., Sugiyama, T., Kusumoto, S., Shirai, T., et al. (2009). Patient Willingness to Undergo Chemotherapy and Thoracic Radiotherapy for Locally Advanced Non-small Cell Lung Cancer. *Psychooncology* 18 (5), 483–489. doi:10.1002/pon.1450

Janssens, R., Huys, I., van Overbeeke, E., Whichello, C., Harding, S., Kübler, J., et al. (2019a). Opportunities and Challenges for the Inclusion of Patient Preferences in the Medical Product Life Cycle: a Systematic Review. *BMC Med. Inform. Decis. Mak* 19 (1), 189. doi:10.1186/s12911-019-0875-z

Janssens, R., Russo, S., van Overbeeke, E., Whichello, C., Harding, S., Kubler, J., et al. (2019b). *Patient Preferences in the Medical Product Life Cycle: What Do Stakeholders Think? Semi-structured Qualitative Interviews in Europe and the USA*. Patient. Available at: https://link.springer.com/article/10.1007/s40271-019-00367-w#citeas

King-Kallimanis, B. L., Howie, L. J., Roydhouse, J. K., Singh, H., Theoret, M. R., Blumenthal, G. M., et al. (2019). Patient Reported Outcomes in Anti-PD-1/pd-L1 Inhibitor Immunotherapy Registration Trials: FDA Analysis of Data Submitted and Future Directions. *Clin. Trials* 16 (3), 322–326. doi:10.1177/1740774519836991

Kurita, K., Garon, E. B., Stanton, A. L., and Meyerowitz, B. E. (2013). Uncertainty and Psychological Adjustment in Patients with Lung Cancer. *Psychooncology* 22 (6), 1396–1401. doi:10.1002/pon.3155

Lacey, A., and Luff, D. (2007). *Qualitative Research Analysis: The NIHR RDS for the East Midlands*. Yorkshire & the Humber. Available at: https://www.rds-yh.nihr.ac.uk/wp-content/uploads/2013/05/9_Qualitative_Data_Analysis_Revision_2009.pdf

Maric, D., Jovanovic, D., Golubicic, I., Dimic, S., and Pekmezovic, T. (2010). Health-related Quality of Life in Lung Cancer Patients in Serbia: Correlation with Socio-Economic and Clinical Parameters. *Eur. J. Cancer Care (Engl)* 19 (5), 594–602. doi:10.1111/j.1365-2354.2009.01101.x

Marzorati, C., and Pravettoni, G. (2017). Value as the Key Concept in the Health Care System: How it Has Influenced Medical Practice and Clinical Decision-Making Processes. *J. Multidiscip Healthc.* 10, 101–106. doi:10.2147/JMDH.S122383

Patient Preference Information – Voluntary Submission (2016). *Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Department of Health and Human Services. Food and Drug Administration*. Rockville, MD: Center for Devices and Radiological Health and Center for Biologics Evaluation and Research. Available at: https://www.fda.gov/media/92593/download

Patient-Focused Drug Development (2018). *Collecting Comprehensive and Representative Input - Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders - GUIDANCE. U.S. Department of Health and Human Services Food and Drug Administration CfDEaRC*. Center for Biologics Evaluation and Research (CBER). Available at: https://www.fda.gov/media/139088/download

Petrocchi, S., Janssens, R., Oliveri, S., Arnou, R., Durosini, I., Guiddi, P., et al. (2021). What Matters Most to Lung Cancer Patients? A Qualitative Study in Italy and Belgium to Investigate Patient Preferences. *Front. Pharmacol.* 12 (80), 602112. doi:10.3389/fphar.2021.602112

Prefer (2020). Patient Preferences. Available from: https://www.imi-prefer.eu/.

Remon, J., Passiglia, F., Ahn, M. J., Barlesi, F., Forde, P. M., Garon, E. B., et al. (2020). Immune Checkpoint Inhibitors in Thoracic Malignancies: Review of the Existing Evidence by an IASLC Expert Panel and Recommendations. *J. Thorac. Oncol.* 15 (6), 914–947. doi:10.1016/j.jtho.2020.03.006

Rowland, C., Danson, S. J., Rowe, R., Merrick, H., Woll, P. J., Hatton, M. Q., et al. (2016). Quality of Life, Support and Smoking in Advanced Lung Cancer Patients: a Qualitative Study. *BMJ Support. Palliat. Care* 6 (1), 35–42. doi:10.1136/bmjspcare-2013-000589

Schmidt, K., Damm, K., Prenzler, A., Golpon, H., and Welte, T. (2016). Preferences of Lung Cancer Patients for Treatment and Decision-Making: a Systematic Literature Review. *Eur. J. Cancer Care (Engl)* 25 (4), 580–591. doi:10.1111/ecc.12425

Schmidt, K., Damm, K., Vogel, A., Golpon, H., Manns, M. P., Welte, T., et al. (2017). Therapy Preferences of Patients with Lung and colon Cancer: a Discrete Choice experiment. *Patient Prefer Adherence* 11, 1647–1656. doi:10.2147/PPA.S138863

Soekhai, V., Whichello, C., Levitan, B., Veldwijk, J., Pinto, C. A., Donkers, B., et al. (2019). Methods for Exploring and Eliciting Patient Preferences in the Medical Product Lifecycle: a Literature Review. *Drug Discov. Today* 24 (7), 1324–1331. doi:10.1016/j.drudis.2019.05.001

Sugitani, Y., Sugitani, N., and Ono, S. (2020). Quantitative Preferences for Lung Cancer Treatment from the Patients' Perspective: A Systematic Review. *Patient* 13 (5), 521–536. doi:10.1007/s40271-020-00434-7

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (Ich) (2020). *ICH Reflection Paper on*

Proposed ICH Guideline Work to advance Patient Focused Drug Development, 5.
US Food and Drug Administration (2006). Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Available from: https://www.fda.gov/media/77832/download.
Us Food and Drug Administration (2016). *Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling.* [29].
US Food and Drug Administration (2020). *Patient Preference-Sensitive Areas: Using Patient Preference Information in Medical Device Evaluation.*
Van Der Weijst, L., Lievens, Y., Schrauwen, W., and Surmont, V. (2019). Health-Related Quality of Life in Advanced Non-small Cell Lung Cancer: A Methodological Appraisal Based on a Systematic Literature Review. *Front. Oncol.* 9, 715. doi:10.3389/fonc.2019.00715
van Overbeeke, E., Janssens, R., Whichello, C., Schölin Bywall, K., Sharpe, J., Nikolenko, N., et al. (2019). Design, Conduct, and Use of Patient Preference Studies in the Medical Product Life Cycle: A Multi-Method Study. *Front. Pharmacol.* 10, 1395. doi:10.3389/fphar.2019.01395
van Overbeeke, E., Whichello, C., Janssens, R., Veldwijk, J., Cleemput, I., Simoens, S., et al. (2019). Factors and Situations Influencing the Value of Patient Preference Studies along the Medical Product Lifecycle: a Literature Review. *Drug Discov. Today* 24 (1), 57–68. doi:10.1016/j.drudis.2018.09.015
Walsh, C. A., and Al Achkar, M. (2021). A Qualitative Study of Online Support Communities for Lung Cancer Survivors on Targeted Therapies. *Support Care Cancer* 29, 4493–4500. doi:10.1007/s00520-021-05989-1
Whichello, C., van Overbeeke, E., Janssens, R., Schölin Bywall, K., Russo, S., Veldwijk, J., et al. (2019). *Factors and Situations Affecting the Value of Patient Preference Studies: Semi-structured Interviews in Europe and the US Frontiers in Pharmacology.*

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Long-Term Use of Statins Lowering the Risk of Rehospitalization Caused by Ischemic Stroke Among Middle-Aged Hyperlipidemic Patients: A Population-Based Study

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Background: The long-term effects of statin use on rehospitalization due to ischemic stroke (reHospIS) in hyperlipidemic patients are still unknown. Therefore, we aimed to assess the long-term risks of reHospIS for hyperlipidemic patients who were taking statins and nonstatin lipid-lowering medicines on a regular basis.

Methods and Materials: The National Health Insurance Research Database in Taiwan was used to conduct a 6-year cohort study of patients >45 years old (n = 9,098) who were newly diagnosed with hyperlipidemia and hospitalized for the first or second time due to ischemic stroke (IS). The risk of reHospIS was assessed using Cox proportional hazards regression model.

Results: Nonstatin lipid-lowering medicines regular users were associated with a higher risk of reHospIS compared to stains users (hazard ratio, HR = 1.29–1.39, $p < 0.05$). Rosuvastatin was the most preferred lipid-lowering medicine with lower HRs of reHospIS

Abbreviations: IS, ischemic stroke; reHospIS, rehospitalization due to IS; HF, heart failure; HBP, high blood pressure; PAOD, peripheral arterial occlusion disease.

in hyperlipidemic patients whether they developed diabetes or not. Bezafibrate regular users of hyperlipidemic patients developing diabetes (HR = 2.15, $p < 0.01$) had nearly 50% lower reHospIS risks than those without diabetes (HR = 4.27, $p < 0.05$). Age, gender, drug dosage, comorbidities of diabetes and heart failure (HF), and characteristics of the first hospitalization due to IS were all adjusted in models. Moreover, increasing trends of HRs of reHospIS were observed from Rosuvastatin, nonstatin lipid-lowering medicines, Lovastatin, and Gemfibrozil to Bezafibrate users.

Conclusion: Statins were associated with long-term secondary prevention of reHospIS for hyperlipidemic patients. Rosuvastatin seemed to have the best protective effects. On the other hand, Bezafibrate appears to be beneficial for hyperlipidemic patients developing diabetes. Further research into the combination treatment of statin and nonstatin lipid-lowering medicines in hyperlipidemic patients developing diabetes is warranted.

Keywords: statins, lipid-lowering medicines, rehospitalization, hyperlipidemia, ischemic stroke, secondary prevention, diabetes mellitus

INTRODUCTION

Hyperlipidemia is one of the most prevalent risk factors for atherosclerosis and cardioembolic stroke (Ayata et al., 2013), particularly in patients with high LDL cholesterol (Farnier and Davignon, 1998; MF, 2021). Ischemic stroke (IS) is a major cause of morbidity and mortality. Elevated LDL levels appear to increase the risk of IS (Tziomalos et al., 2009). Treatment of hyperlipidemia is helpful in both primary and secondary prevention of coronary heart disease and stroke (Arshad, 2014).

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the most commonly prescribed lipid-lowering medicines (Bonetti et al., 2003). They have been shown to reduce the risk of IS in patients with a history of IS (Tziomalos et al., 2009) via the lipid-lowering effect (Farnier and Davignon, 1998) and the reduction of platelet activation and reactivity (Pawelczyk et al., 2015). Statin-based lipid lowering is effective for both primary and secondary prevention of IS (Milionis et al., 2020; Zhu et al., 2020). In addition, statin pretreatment or use in the acute phase of IS improved outcomes for recurrence, cardiovascular events (Farnier and Davignon, 1998; Flint et al., 2012a; Kim et al., 2014; O'Brien et al., 2015; Guo et al., 2015; Scheitz et al., 2015; Yeramaneni et al., 2017; Cui et al., 2020; Furlan et al., 2020; Wang et al., 2020), neurological disability, and all-cause and cardiovascular mortality (Orkaby et al., 2020). Statins are the first-line LDL-lowering therapy in diabetic patients. Studies indicated that adding nonstatin lipid-lowering medicines to statins could improve the lipid profile (Scicali et al., 2018) and reduce adverse cardiovascular events (NAEEM et al., 2018) in diabetic individuals.

However, most previous studies (Flint et al., 2012b; Koton et al., 2012) compared the short-term protective effects of statin users, inpatient statin users, or pre-IS stroke statin users to statin-naïve users. To the best of our knowledge, no long-term follow-up studies have been conducted to evaluate the risk of rehospitalization due to ischemic stroke (reHospIS) in hyperlipidemic patients with or without diabetes who were regularly taking statins or other nonstatin lipid-lowering medicines.

METHODS AND MATERIALS

Study Population and Study Design

The coverage rate of National Health Insurance is nearly 100% in Taiwan. The analysis data is from the National Health Insurance Research Database (NHIRD) and capable of representing the whole nation. This is a cohort study and we included the medical claims from 2005 to 2010 in the ICD-9-CM system. During the study period in Taiwan, the clinical description guideline of lipid-lowering medicines was consistent. The eligible criteria of the study population were 1) the new patients with newly diagnosed disorders of lipid metabolism (ICD-9-CM code: 272), 2) the first hospitalization due to IS (ICD-9-CM code: 434 and 437 of inpatient medical records) from 2005 to 2009, 3) taking monolipid-lowering medicine over 90 days and at least three times outpatient visits for hyperlipidemia after the first hospitalization due to IS, 4) age larger than 45 years at which IS likely to occur (Yousufuddin and Young, 2019), 5) the period of time between first and second hospitalization larger than 1 year, and 6) the defined daily dose (DDD) over zero. We excluded the inpatients 1) whose hospitalization cause was car incidents or suicide and 2) who were discharged from the hospitals for the reasons of suicide, death, or about to die. In the end, 9,098 patients are eligible (**Figure 1**). To diminish the impact of baseline difference of putative confounders, we designed a 1-year washout period prior to the start of the study. Patients who were diagnosed with disorders of lipid metabolism (ICD-9-CM code: 272), ischemic diseases (ICD-9-CM code: 410–414), or cerebrovascular diseases (ICD-9-CM code: 430–438) or who were hospitalized due to IS in 2004 were excluded. Since 2001, the ICD-9-CM system had not been updated (Administration, 2014). Throughout the study period, the diagnosis classification system remained the same. This study was exempted from full review following consultation with the Tri-Service General Hospital Institutional Review Board (TSGH IRB No. B–110–22).

Blood Lipid-Lowering Medicines

Nine blood lipid-lowering medicines were included (Atorvastatin, Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Bezafibrate, Gemfibrozil, and

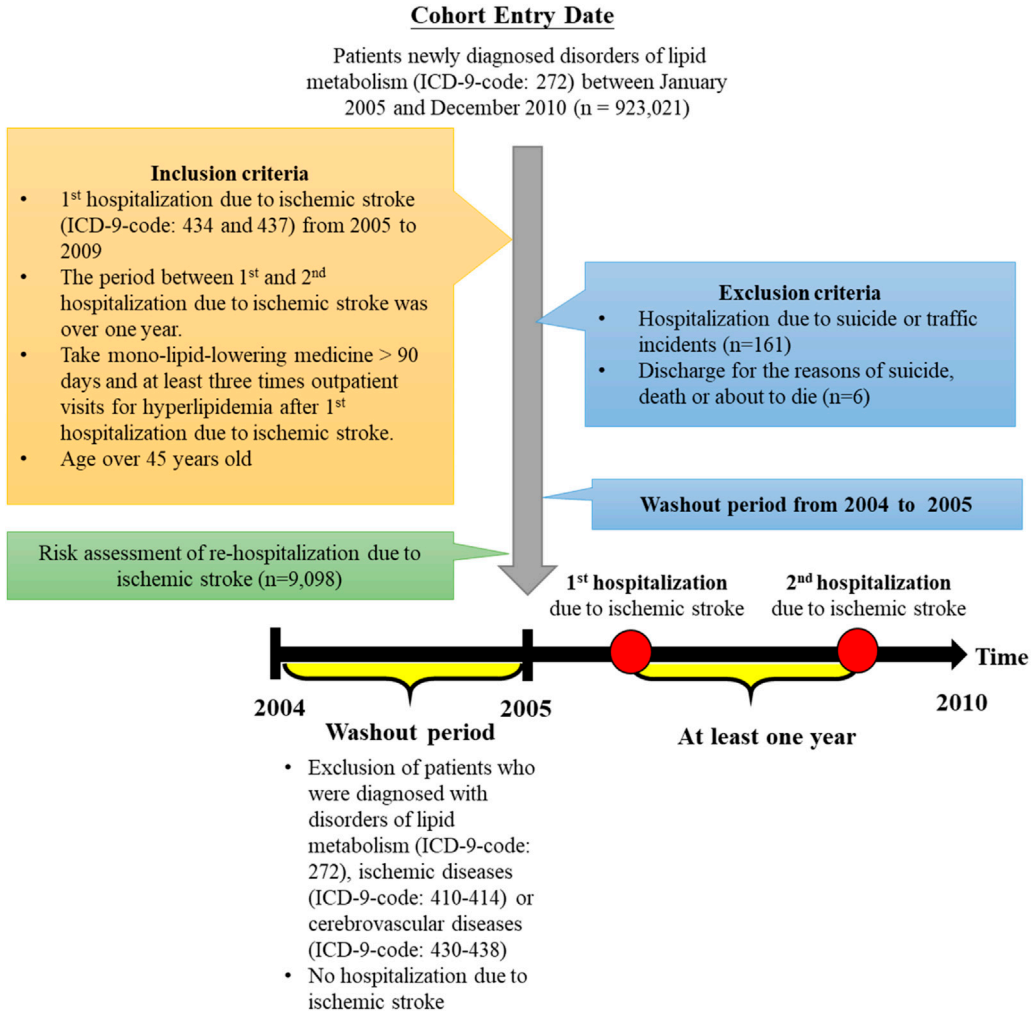

FIGURE 1 | Study workflow.

Fenofibrate). In order to understand the effects of various types of lipid-lowering medicines on the risks of reHospIS, all hyperlipidemic patients were divided into four subgroups according to the type of monolipid-lowering medicine they used on a regular basis: (A) nonstatin lipid-lowering medicines and statins regular users; (B) high-density statins (Atorvastatin, Rosuvastatin, and Simvastatin), nonstatin lipid-lowering medicines (Bezafibrate, Gemfibrozil, and Fenofibrate), and statins regular users; (C) Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Bezafibrate, Gemfibrozil, Fenofibrate, and Atorvastatin regular users; (D) five individual statins (Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, and Fluvastatin) and nonstatin lipid-lowering medicine regular users.

The Definition of Monolipid-Lowering Medicine Regular Users

Patients who had been prescribed a single type of lipid-lowering medicine for more than 90 days and had at least three times records of outpatient visits from the first hospitalization due to IS to the end of follow-up were classified as monolipid-lowering medicine regular users. In order to clarify the effect of every single type of medication on rehospitalization, patients who used different types of blood lipid-lowering medicines in combination were excluded.

The Definition of DDD, Compliance Rate, and Comorbidity Diseases

The definition of DDD from WHO is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose (WHO, 2020). The values ranged from 0 to 1. The DDD was calculated between the first hospitalization date due to IS and the end of follow-up.

Compliance rates of lipid-lowering medicines were calculated as the number of days with lipid-lowering medicines supply

TABLE 1 | Descriptive statistics of study population.

	Rehospitalization due to ischemic stroke (*n* = 9,098)					
	No (*n* = 8,530)		Yes (*n* = 568)		Hazard ratio	*p* values
	N	%	*n*	%		
Follow-up time (days, mean, and SD)	1,241	504	935	405		
Year of first-time hospitalization[%]						
2005	1,353	0.16	173	0.30	ref	
2006	1756	0.21	178	0.31	0.97	0.80
2007	1836	0.22	137	0.24	1.02	0.87
2008	1886	0.22	63	0.11	0.77	0.09
2009	1,699	0.20	17	0.03	0.65	0.11
Demographic characteristics						
Age (year, mean, and SD)	64	11	65	10.00	1.01	*
Gender						
Male	4,963	0.58	350	0.62	ref	
Female	3,567	0.42	218	0.38	0.85	0.06
The total cost of first-time hospitalization due to ischemic stroke (United States dollars)[&]						
<667	2,348	0.27	144	0.25	ref	
667–1,000	2,314	0.27	153	0.27	1.12	0.34
1,000–1,333	1,461	0.17	95	0.17	1.12	0.38
≥1,333	2,407	0.28	176	0.31	1.27	*
The total days of first-time hospitalization due to ischemic stroke						
<4	1,216	0.14	73	0.13	ref	
4–7	2,963	0.35	176	0.31	1.00	0.99
7–10	1918	0.22	123	0.22	1.07	0.63
≥10	2,433	0.29	196	0.35	1.33	*
Hospital type						
Public	1855	0.22	137	0.24	ref	
Private	1838	0.22	127	0.22	0.86	0.23
Nonprofit proprietary	4,837	0.57	304	0.54	0.91	0.36
Hospital class						
Medical center	3,546	0.42	205	0.36	ref	
Regional hospital	3,973	0.47	279	0.49	1.21	*
District hospital	1,011	0.12	84	0.15	1.34	*
Location of hospitals						
Taipei capital	2,356	0.28	144	0.25	ref	
Northern	1,144	0.13	85	0.15	1.20	0.18
Central	1,347	0.16	98	0.17	1.19	0.18
Southern	1,467	0.17	99	0.17	1.12	0.38
Southern remote	1877	0.22	121	0.21	1.01	0.95
Eastern	339	0.04	21	0.04	1.03	0.90
Compliance						
DDD						
≤0.1	3,473	0.41	178	0.31	ref	
0.1–0.2	2,523	0.30	182	0.32	1.94	***
0.2–0.3	1248	0.15	84	0.15	2.06	***
0.3–0.4	568	0.07	51	0.09	2.82	***
0.4–0.5	320	0.04	18	0.03	1.95	**
>0.5	398	0.05	55	0.10	4.79	***
Compliance rate						
≤0.25	5,220	0.61	318	0.56	ref	
0.25–0.5	2,551	0.30	156	0.27	1.51	***
>0.5	759	.09	94	0.17	3.16	***
Comorbidities						
High blood pressure (HBP)	6,066	0.71	412	0.73	0.90	0.27
Angina	617	0.07	44	0.08	0.94	0.71
Diabetes mellitus (DM)	2,840	0.33	240	0.42	1.31	**
Heart failure (HF)	87	0.01	12	0.02	1.85	*
Peripheral arterial occlusion disease (PAOD)	604	0.07	46	0.08	1.04	0.80
Arrhythmics	78	0.01	8	0.01	1.52	0.24

****p value < 0.001, **p value < 0.01, *p value < 0.05. Statistical analysis was using univariable Cox proportional hazards regression. ref: reference group and The cost was converted from NT dollars to Unites States dollars at a 30 to one exchange rate. % The period between first hospitalization and second hospitalization due to ischemic stroke was set to be over 1 year, thus no first hospitalization due to ischemic stroke was present in 2010.*

divided by the total number of days from the first hospitalization date due to IS to the end of follow-up (Wei et al., 2002).

In NHIRD, there is a risk of misclassification bias due to unverified diagnosis coding (Hsieh et al., 2019). As a result, we defined diabetes mellitus (DM) hyperlipidemic patients as those who received medications of comorbidity diseases for over 90 days after the first hospitalization due to IS were defined as having such comorbidity disease. We included the already known comorbidity diseases to IS, i.e., high blood pressure, angina, DM, HF, peripheral arterial occlusion disease, and arrhythmics. Type II diabetes accounted for 99 percent of all diabetes cases in Taiwan. As a result, diabetes was not divided into type I and type II diabetes (National Institutes of He, 2019).

Statistical Analysis

We used a univariable Cox proportional hazards regression model to explore the association of all indicators, including lipid-blood lowering medicines, characteristics of hospitals, cost of hospitalization, demographic characteristics, and comorbidity diseases with reHospIS. Multiple prediction models of lipid-blood lowering medicines on reHospIS were constructed under the adjustment of significant covariates or confounders by using multivariable Cox proportional hazard model regression. The level of statistical significance was set to be a two-sided p value less than 0.05. In the sensitivity analysis, all the hyperlipidemic patients were categorized into four patient subgroups of 1) all hyperlipidemic patients, 2) hyperlipidemic patients with diabetes, 3) nondiabetes hyperlipidemic patients, and 4) nondiabetes and non-HF hyperlipidemic patients. The case number of hyperlipidemic patients with HF was limited (n = 99) for further subgrouping and meaningful multivariable statistical analysis (**Table 1**). Therefore, we did not group study patients by HF. However, we wanted to know the lipid-lowering effects for hyperlipidemic patients without these two comorbidity diseases, and we presented the subgroup of nondiabetes and non-HF hyperlipidemic patients.

RESULTS

The Risk Factors of reHospIS

Older age, male sex, higher total cost of first-time hospitalization, higher total days of first-time hospitalization, lower hospital class, developing diabetes and heart failure (HF), and higher DDD and compliance rate were the risk factors of reHospIS (**Table 1**). DDD and compliance rates tended to indicate the severity of IS in the dose-response effect. Perhaps this is why DDD and compliance rates are positively associated with reHospIS risks.

The Risks of reHospIS for Hyperlipidemic Patients Taking Monolipid-Lowering Medicine

Hyperlipidemic patients were grouped into four subgroups by the type of monolipid-lowering medicine they took regularly. Four medicine categories were (A) nonstatin lipid-lowering medicines versus statins (served as the reference group in the model, abbreviated as ref), (B) high-density statins (Atorvastatin, Rosuvastatin, and Simvastatin) and nonstatin lipid-lowering medicines (Bezafibrate, Gemfibrozil, and Fenofibrate) versus statins (ref), (C) Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Bezafibrate, Gemfibrozil, and Fenofibrate versus Atorvastatin (ref), and (D) five individual statins of Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, and Fluvastatin versus nonstatin lipid-lowering medicines (ref).

In the univariable Cox proportional hazards regression models of four medicine categories (**Figure 2**), Rosuvastatin regular users had a significantly lower risk of reHospIS (HR = 0.76, $p < 0.05$) than Atorvastatin in subgroups (C) and (D) (**Figure 2**). Among subgroups (A) to (D), the other lipid-lowering medicines had no significant difference in the risks of reHospIS among each other (**Figure 2**).

Multivariable Cox Proportional Hazards Regression Model

We entered all significant factors from univariable Cox proportional hazards regression models (**Table 1**) and furtherly analyzed them using multivariable Cox proportional hazard regression models. In the sensitivity analysis of evaluating risks of reHospIS, all hyperlipidemic patients are categorized into four patient subgroups: 1) all hyperlipidemic patients, 2) hyperlipidemic patients with diabetes, 3) hyperlipidemic patients without diabetes, and 4) hyperlipidemic patients without diabetes and without HF.

In the results of medicine subgroups (A) to (D), Rosuvastatin regular users had the lowest HRs of reHospIS ranging from 0.63 to 0.64 ($p < 0.05$) for all patients subgroups (**Figure 3**). Statins regular users had significantly lower risks (HRs = 1.2–1.4) for all patient subgroups as compared with nonstatin lipid-lowering medicines (**Figure 3A**). Diabetes patients who took nonstatin lipid-lowering medicines had higher risks of reHospIS as compared with those who took low-density statins. There was no statistically significant difference in the risk of reHospIS for all patient subgroups who took low- or high-density statins (**Figure 3B**). Rosuvastatin regular users of all patient subgroups had the significantly lowest HRs of reHospIS ranging from 0.63 to 0.65 ($p < 0.05$) as compared with Atorvastatin regular users in subgroups (C) and (D) (**Figures 3C,D**). Lovastatin is one type of statin. Except for the diabetes patient subgroup, the other patient subgroups who took Lovastatin (HR = 1.56–1.78 $p < 0.05$) rather than the other types of statins had the highest risk as compared with Atorvastatin regular users (**Figures 3C,D**). Except for diabetes patient subgroups, Bezafibrate regular users had significantly higher risks of reHospIS (HR = 2.39–4.3, $p < 0.05$) (**Figure 3C**). To rule out the possible confounding effect of IS severity, we excluded patients who were not likely to be severe IS patients by excluding low-density statin regular users (the case number of analysis 6,479) (**Supplementary Table S1**). The abovementioned results remain consistent. **Figure 4** depicted the increasing risk trends of reHospIS among regular users of Rosuvastatin, Atorvastatin, nonstatin lipid-lowering medicines, Lovastatin, Gemfibrozil, and Bezafibrate. Except for Bezafibrate, the HR of each blood lipid-lowering medicine in each patient subgroup was similar (**Figure 4**).

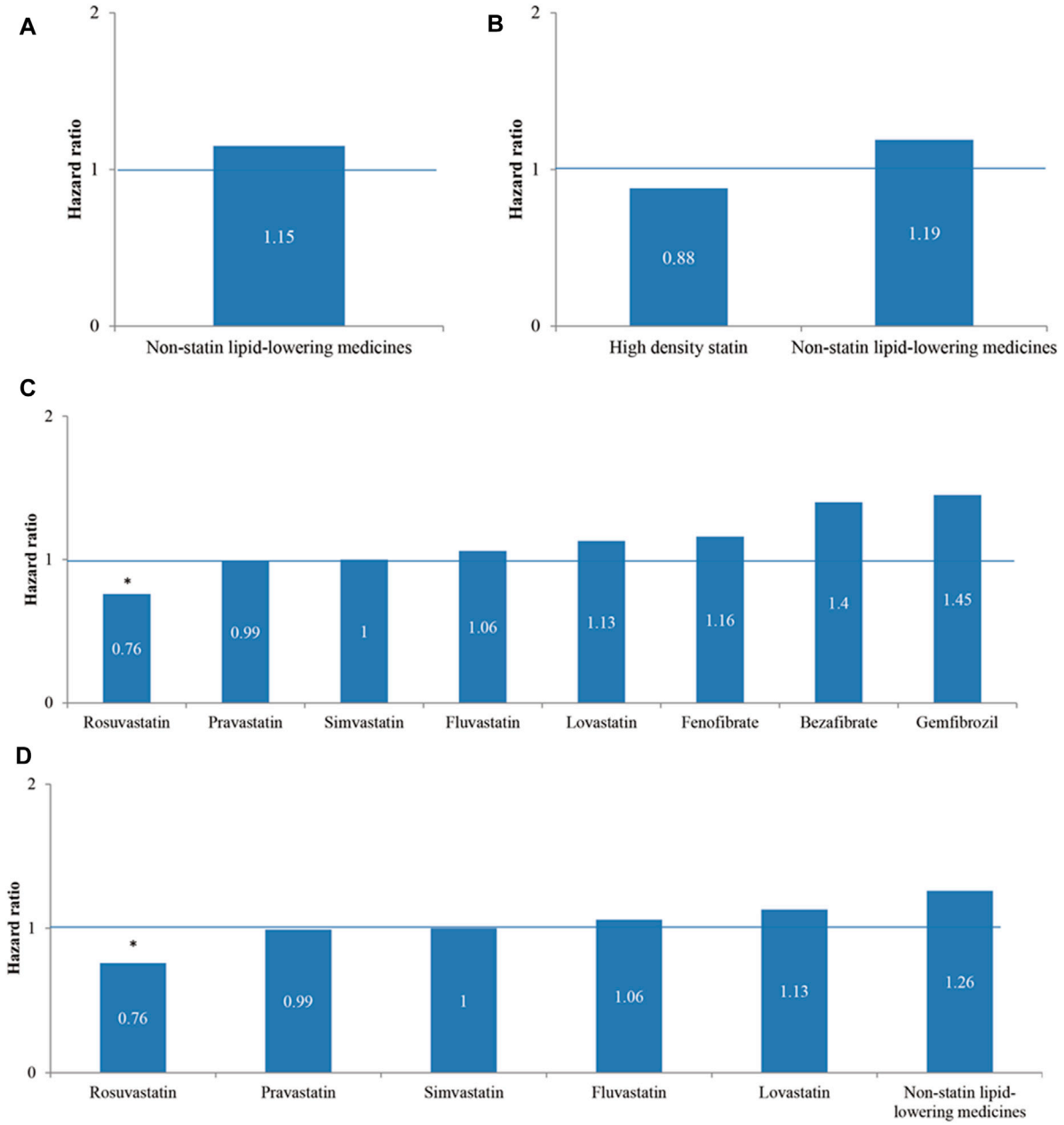

FIGURE 2 | The hazard ratios of rehospitalization due to ischemic stroke (reHospIS) for hyperlipidemic patients grouped by categories of lipid-lowering medicines they took regularly using univariable Cox proportional hazards regression. **(A)** Nonstatin lipid-lowering medicines versus statins (reference group, ref); **(B)** high-density statins (Atorvastatin, Rosuvastatin, and Simvastatin) and nonstatin lipid-lowering medicines versus low-density statins (Bezafibrate, Gemfibrozil, and Fenofibrate) (ref); **(C)** Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Bezafibrate, Gemfibrozil, and Fenofibrate versus Atorvastatin (ref); **(D)** five individual statins of Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, and Fluvastatin versus nonstatin lipid-lowering medicines (ref). The asterisk represents a statistically significant hazard ratio ($p < 0.05$).

Bezafibrate and Lovastatin Users With DM Have Lower Risk Than Those Without DM

Though Bezafibrate was linked to a higher risk of reHospIS when compared to Atorvastatin, it appeared to be beneficial to hyperlipidemic patients with diabetes (HR = 2.15, $p < 0.05$) than none DM patients (HR = 4.27, $p < 0.05$) by reducing nearly half the risk of reHospIS. There was no statistical difference of risks of reHospIS in the DM patient subgroup who took Lovastatin (HR = 1.31 $p = 0.40$) or Atorvastatin, whereas Lovastatin was linked to a higher risk of reHospIS for nondiabetes hyperlipidemic patients (HR = 1.8, $p < 0.05$) when compared to Atorvastatin (**Figure 3C**).

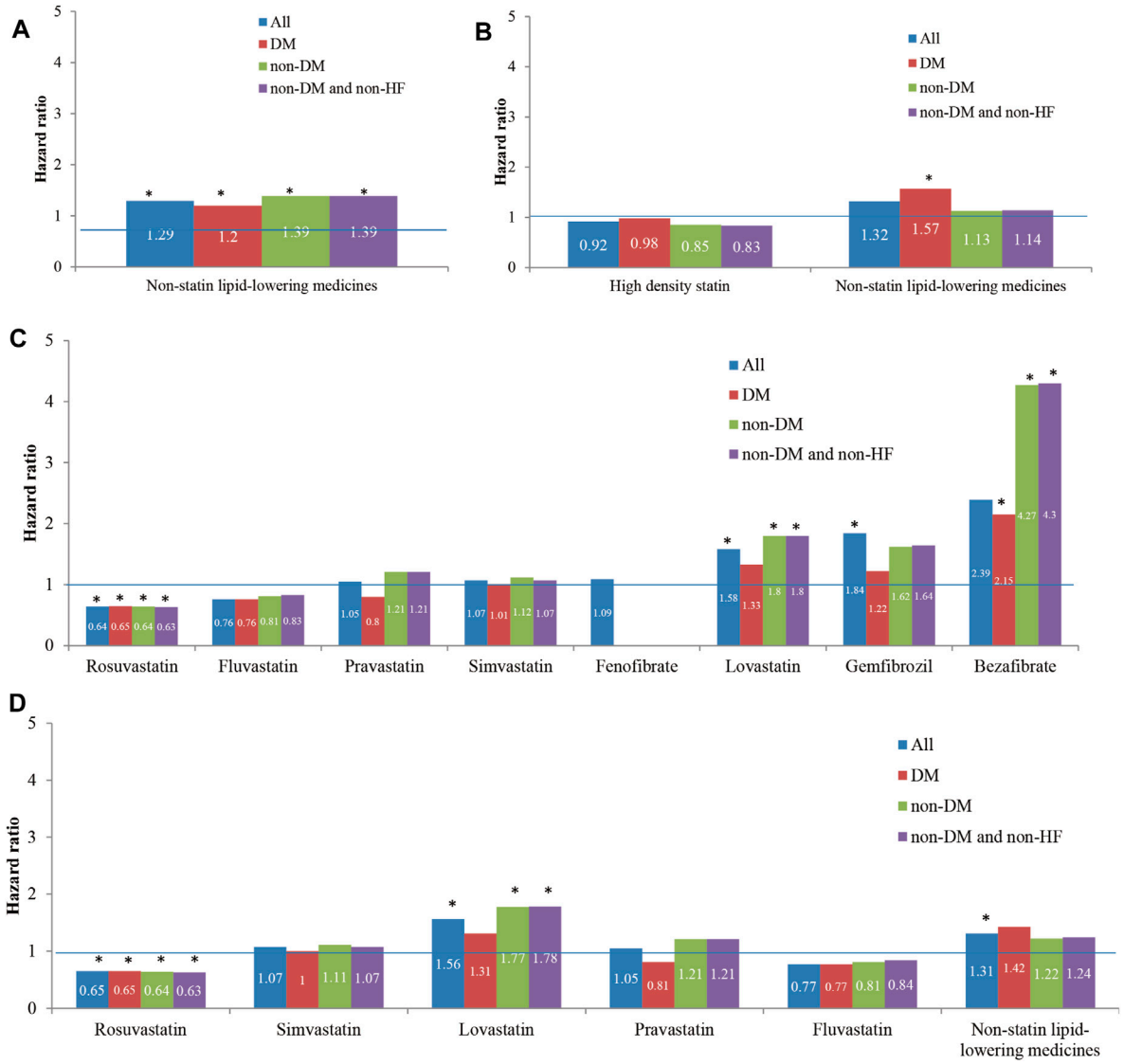

FIGURE 3 | The hazard ratios of reHospIS for hyperlipidemic patients grouped by comorbidities (diabetes mellitus, DM, and heart failure, HF) and categories of lipid-lowering medicines they took regularly using multivariable Cox proportional hazards regression. All the hyperlipidemic patients were categorized into four patient subgroups of 1) all hyperlipidemic patients, 2) hyperlipidemic patients with DM, 3) non-DM hyperlipidemic patients, and 4) non-DM and non-HF hyperlipidemic patients. Cox proportional hazards regression model of each medicine category was conducted for each patient subgroup. The medicine categories were described as follows: **(A)** nonstatin lipid-lowering medicines versus statins (reference group, ref); **(B)** high-density statins (Atorvastatin, Rosuvastatin, and Simvastatin) and nonstatin lipid-lowering medicines versus low-density statins (Bezafibrate, Gemfibrozil, and Fenofibrate) (ref); **(C)** Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Bezafibrate, Gemfibrozil, and Fenofibrate versus Atorvastatin (ref); **(D)** five individual statins of Rosuvastatin, Simvastatin, Lovastatin, Pravastatin, and Fluvastatin versus nonstatin lipid-lowering medicines (ref). The asterisk represents a statistically significant hazard ratio ($p < 0.05$). Significant variables in the univariable Cox proportional hazards regression models were selected and entered in the multiple Cox proportional hazards regression model.

Summary

Under the adjustments of confounders, statins have a lower risk of reHospIS than nonstatin lipid-lowering medicines users in all subgroups. Among these lipid-lowering medicines, regular Rosuvastatin users had the lowest HRs of reHospIS. Though Bezafibrate and Lovastatin were linked to higher risks of reHospIS, they may be beneficial to DM patients when compared to none DM patients.

DISCUSSION

This is a 6-years long retrospective study of 9,098 hyperlipidemic patients. Long-term statin users of hyperlipidemic patients had lower reHospIS risks than nonstatin lipid-lowering medicines users. In comparison to Atorvastatin regular users, Rosuvastatin regular users had the lowest HRs of reHospIS among all patient subgroups. Except for hyperlipidemic patients with diabetes, regular Lovastatin users had the highest risks of reHospIS

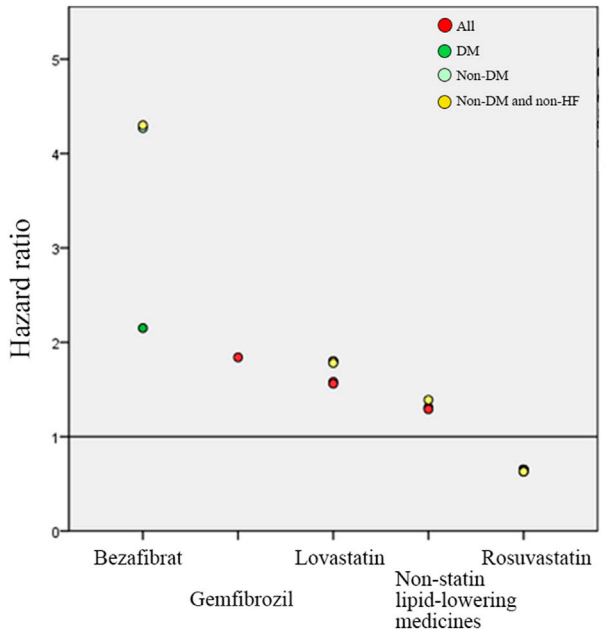

FIGURE 4 | Multivariable Cox hazard ratio regression outcomes of lipid-lowering medicines on predicting the risk of reHospIS. Only significant lipid-lowering medicines are presented. Atorvastatin users were served as the reference group, the horizontal line of value one. There are four hyperlipidemic patient subgroups marked in different colored circles. The red circle is all hyperlipidemic patients (All). The green circle is hyperlipidemic patients with diabetes (DM). The light green circle is non-DM hyperlipidemic patients. The yellow circle is non-DM and none-HF hyperlipidemic patients.

among statins regular users. The increasing trends of risks of reHospIS were observed from Rosuvastatin, nonstatin lipid-lowering medicines, Lovastatin, and Gemfibrozil to Bezafibrate regular users.

The mechanism of statins primarily lowered the concentration of LDL rather than reducing TG or increasing HDL. Randomized trials have shown that lowering LDL cholesterol reduces the risk of stroke (Castilla-Guerra et al., 2019). It may be the reason that statins are more protective against reHospIS than nonstatin lipid-lowering medicines users. The first-generation statins are Pravastatin, Lovastatin, and Fluvastatin; the second-generation statins are Simvastatin and Atorvastatin; and the third-generation statins are Rosuvastatin and Pitavastatin. Second- and third-generation statins were more effective at lowering LDL cholesterol than first-generation statins. In addition, Rosuvastatin outperformed Atorvastatin, Simvastatin, and Pravastatin in terms of LDL-lowering efficacy.

In a mouse experiment, both normal and high doses of Rosuvastatin were found to be effective in preventing rt-PA-associated hemorrhages with brain ischemia while having no effect on cerebral blood reflow or neural function (Lu et al., 2018). In addition, Rosuvastatin slowed the progression of cardiovascular disease in diabetes patients by improving HDL functions and suppressing inflammation. The prevention of unfavorable outcomes of IS was associated not only with LDL-lowering effect but also with pleiotropic effects of endothelial function, modulating thrombogenesis, attenuating inflammatory and oxidative stress damage, and facilitating angiogenesis matters (Zhao et al., 2014).

It was noted that nonstatin lipid-lowering medicines were linked to higher risks of reHospIS in none-diabetes hyperlipidemic patients. Statins are preferred as first-line therapy, and other lipid-lowering medicines should be avoided. However, it has been reported that the combination therapy of statin and nonstatin lipid-lowering medicines (e.g., ezetimibe, fibrates, bile acid sequestrants, PCSK9 inhibitors, and omega-3 fatty acids) (Rodriguez et al., 2018) was recommended for releasing other syndromes. For instance, the combination of Simvastatin and Bezafibrate increased cholesterol efflux in parallel with HDL cholesterol and apoA-I responses. When compared to statin treatment alone, Bezafibrate and statin combination therapy reduces the risk of 30-day major adverse cardiovascular events and 1-year mortality rates in diabetes patients.

In this study, Bezafibrate regular users with diabetes had nearly 50% lower reHospIS risks than those without diabetes. Bezafibrate is one of the most commonly used molecules in the treatment of hypertriglyceridemia, and statin therapy is often added to achieve lipid profile goals in mixed dyslipidemia (León-Martínez et al., 2021). Bezafibrate ameliorates diabetes and may benefit patients with nonalcoholic fatty liver disease and impaired glucose metabolism by reducing steatosis, enhancing hepatic mitochondrial mass, improving metabolic flexibility, and increasing hepatic insulin sensitivity (Franko et al., 2017).

Lovastatin was an unfavorable lipid-lowering medicine for nondiabetes hyperlipidemic patients due to its high risk of reHospIS, but it had no adverse effects on those with DM when compared to Atorvastatin. Moreover, Lovastatin was found to significantly reduce fatty streak lesion formation in the aortic arch of hyperlipidemic-diabetic hamsters (El-Swefy et al., 2000). Its other functions of lowering plasma total triglycerides and total cholesterols, selectively decreasing non-HDL-C, and providing antioxidant protection may also contribute to its protective effects. The antioxidant effects of Lovastatin may be beneficial for hyperlipidemic patients with diabetes.

There were some limitations in the study. Not all the statins were included in the study (e.g., Pitavastatin) because some statins were not commercially available and proven by Taiwan Food and Drug Administration during the study period. Serum lipid-lowering herbal medicines, oral hypoglycemic agents, lifestyle, and dietary factors were not included. The use of lipid-lowering medicines, blood lipid levels (not available in the NHIRD), and diabetes status of study subjects prior to their first hospitalization due to IS were not included in the study. However, we designed 1-year washout period prior to the start of the study to reduce the impact of the aforementioned conditions.

We only discussed the risk of reHospIS for users of monolipid-lowering medicines. We are unable to assess the combined effects of statins and nonstatin lipid-lowering medicines. However, we discovered that nonstatin lipid-lowering medicines had a beneficial effect on hyperlipidemic patients with diabetes. It

calls for further studies into the effects of combinational treatments on the long-term risks of reHospIS.

CONCLUSION

In comparison to nonstatin lipid-lowering medicines, statins had a longer-term beneficial effect of secondary prevention of reHospIS for hyperlipidemic patients. Rosuvastatin is the most effective treatment for all subgroups of hyperlipidemic patients. On the other hand, Bezafibrate appears to benefit hyperlipidemic patients with diabetes. The combined effects of statins and nonstatin lipid-lowering medicines on diabetes hyperlipidemic patients warrant further studies to understand the beneficial mechanism.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions. The dataset can be applied from the National Health Insurance Research Database according to the application regulation. Requests to access these datasets should be directed to https://nhird.nhri.org.tw/apply_00. html.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tri-Service General Hospital Institutional Review Board, No. 325, Sec.2, Chenggong Rd., Neihu District, Taipei City 11490, Taiwan. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Data curation, Y-TC; formal analysis, Y-TC; project administration, J-HY and G-SP; resources, J-HY, G-SP, K-HC, W-CC and C-WY; supervision, C-MC and C-WY; writing–original draft, Y-TC; Writing–review and editing, C-MC, K-HC, L-TK, C-CW, W-CT, W-ZL, Y-SW, H-CL, and C-WY.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.741094/full#supplementary-material

REFERENCES

Administration, N. H. I. (2014). edition_ICD-9-CM 2001 Edition and ICD-10-CM/PCS Corresponding Files. 2021. [cited 2021 Aug 22]; Available from.https://www.nhi.gov.tw/Content_List.aspx?n=C1C92AB9ED30A9FD&topn=23C660CAACAA159D.

Arshad, A. R. (2014). Comparison of Low-Dose Rosuvastatin with Atorvastatin in Lipid-Lowering Efficacy and Safety in a High-Risk Pakistani Cohort: an Open-Label Randomized Trial. *J. Lipids* 2014, 875907. doi:10.1155/2014/875907

Ayata, C., Shin, H. K., Dileköz, E., Atochin, D. N., Kashiwagi, S., Eikermann-Haerter, K., et al. (2013). Hyperlipidemia Disrupts Cerebrovascular Reflexes and Worsens Ischemic Perfusion Defect. *J. Cereb. Blood Flow Metab.* 33 (6), 954–962. doi:10.1038/jcbfm.2013.38

Bonetti, P. O., Lerman, L. O., Napoli, C., and Lerman, A. (2003). Statin Effects beyond Lipid Lowering-Aare They Clinically Relevant?. *Eur. Heart J.* 24 (3), 225–248. doi:10.1016/s0195-668x(02)00419-0

Castilla-Guerra, L., Fernandez-Moreno, M. D. C., Leon-Jimenez, D., and Rico-Corral, M. A. (2019). Statins in Ischemic Stroke Prevention: What Have We Learned in the Post-SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) Decade?. *Curr. Treat. Options. Neurol.* 21 (5), 22. doi:10.1007/s11940-019-0563-4

Cui, C., Dong, S., Chen, N., Bao, J., and He, L. (2020). Low-dose Statin Pretreatment Improves Function and Prognosis of Recurrent Ischemic Stroke Patients. *Ther. Adv. Neurol. Disord.* 13, 1756286420920078. doi:10.1177/1756286420920078

El-Swefy, S., Schaefer, E. J., Seman, L. J., van Dongen, D., Sevanian, A., Smith, D. E., et al. (2000). The Effect of Vitamin E, Probucol, and Lovastatin on Oxidative Status and Aortic Fatty Lesions in Hyperlipidemic-Diabetic Hamsters. *Atherosclerosis* 149 (2), 277–286. doi:10.1016/s0021-9150(99)00331-7

Farnier, M., and Davignon, J. (1998). Current and Future Treatment of Hyperlipidemia: the Role of Statins. *Am. J. Cardiol.* 82 (4B), 3J–10J. doi:10.1016/s0002-9149(98)00423-8

Flint, A. C., Kamel, H., Navi, B. B., Rao, V. A., Faigeles, B. S., Conell, C., et al. (2012). Inpatient Statin Use Predicts Improved Ischemic Stroke Discharge Disposition. *Neurology* 78 (21), 1678–1683. doi:10.1212/WNL.0b013e3182575142

Flint, A. C., Kamel, H., Navi, B. B., Rao, V. A., Faigeles, B. S., Conell, C., et al. (2012). Statin Use during Ischemic Stroke Hospitalization Is Strongly Associated with Improved Poststroke Survival. *Stroke* 43 (1), 147–154. doi:10.1161/STROKEAHA.111.627729

Franko, A., Neschen, S., Rozman, J., Rathkolb, B., Aichler, M., Feuchtinger, A., et al. (2017). Bezafibrate Ameliorates Diabetes via Reduced Steatosis and Improved Hepatic Insulin Sensitivity in Diabetic TallyHo Mice. *Mol. Metab.* 6 (3), 256–266. doi:10.1016/j.molmet.2016.12.007

Furlan, N. E., Souza, J. T., Bazan, S. G. Z., Franco, R. J. D. S., Luvizutto, G. J., Gut, A. L., et al. (2020). Association between Statin Use and Mortality Risks during the Acute Phase of Ischemic Stroke in Patients Admitted to an Intensive Care Unit. *Arq Neuropsiquiatr* 78 (3), 158–162. doi:10.1590/0004-282X20190172

Guo, J., Guo, J., Li, J., Zhou, M., Qin, F., Zhang, S., et al. (2015). Statin Treatment Reduces the Risk of Poststroke Seizures. *Neurology* 85 (8), 701–707. doi:10.1212/WNL.0000000000001814

Hsieh, C. Y., Su, C. C., Shao, S. C., Sung, S. F., Lin, S. J., Kao Yang, Y. H., et al. (2019). Taiwan's National Health Insurance Research Database: Past and Future. *Clin. Epidemiol.* 11, 349–358. doi:10.2147/CLEP.S196293

Kim, J. M., Stewart, R., Kang, H. J., Bae, K. Y., Kim, S. W., Shin, I. S., et al. (2014). A Prospective Study of Statin Use and Poststroke Depression. *J. Clin. Psychopharmacol.* 34 (1), 72–79. doi:10.1097/JCP.0000000000000051

Koton, S., Molshatzki, N., Bornstein, N. M., and Tanne, D. (2012). Low Cholesterol, Statins and Outcomes in Patients with First-Ever Acute Ischemic Stroke. *Cerebrovasc. Dis.* 34 (3), 213–220. doi:10.1159/000342302

León-Martínez, J. M., Martínez-Abundis, E., González-Ortiz, M., and Pérez-Rubio, K. G. (2021). Effect of Berberine Plus Bezafibrate Administration on the Lipid Profile of Patients with Mixed Dyslipidemia: A Pilot Clinical Trial. *J. Med. Food* 24 (2), 111–115. doi:10.1089/jmf.2020.0029

Lu, D., Mai, H. C., Liang, Y. B., Xu, B. D., Xu, A. D., and Zhang, Y. S. (2018). Beneficial Role of Rosuvastatin in Blood-Brain Barrier Damage Following Experimental Ischemic Stroke. *Front. Pharmacol.* 9, 926. doi:10.3389/fphar.2018.00926

Hill, M. F., and Bordoni, B. (2021). Hyperlipidemia. 2021 Feb 7 [cited 2021 May 31]; Available from.https://www.ncbi.nlm.nih.gov/books/NBK559182/.

Milionis, H., Ntaios, G., Korompoki, E., Vemmos, K., and Michel, P. (2020). Statin-based Therapy for Primary and Secondary Prevention of Ischemic Stroke: A

Meta-Analysis and Critical Overview. *Int. J. Stroke* 15 (4), 377–384. doi:10.1177/1747493019873594

Naeem, F., Mckay, G., and Fisher, M. (2018). Cardiovascular Outcomes Trials with Non-statin Lipid-Lowering Drugs in Diabetes. *Br. J. Diabetes* 18 (3). doi:10.15277/bjd.2018.180

National Institutes of Health of Taiwan (2019). *Taiwan Diabetes Yearbook 2019*. Available from.https://lib.nhri.edu.tw/NewWeb/nhri/ebook/39000000450002.pdf

O'Brien, E. C., Greiner, M. A., Xian, Y., Fonarow, G. C., Olson, D. M., Schwamm, L. H., et al. (2015). Clinical Effectiveness of Statin Therapy after Ischemic Stroke: Primary Results from the Statin Therapeutic Area of the Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study. *Circulation* 132 (15), 1404–1413. doi:10.1161/CIRCULATIONAHA.115.016183

Orkaby, A. R., Driver, J. A., Ho, Y. L., Lu, B., Costa, L., Honerlaw, J., et al. (2020). Association of Statin Use with All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. *JAMA* 324 (1), 68–78. doi:10.1001/jama.2020.7848

Pawelczyk, M., Chmielewski, H., Kaczorowska, B., Przybyła, M., and Baj, Z. (2015). The Influence of Statin Therapy on Platelet Activity Markers in Hyperlipidemic Patients after Ischemic Stroke. *Arch. Med. Sci.* 11 (1), 115–121. doi:10.5114/aoms.2015.49216

Rodriguez, V., Newman, J. D., and Schwartzbard, A. Z. (2018). Towards More Specific Treatment for Diabetic Dyslipidemia. *Curr. Opin. Lipidol.* 29 (4), 307–312. doi:10.1097/MOL.0000000000000528

Scheitz, J. F., Endres, M., Heuschmann, P. U., Audebert, H. J., and Nolte, C. H. (2015). Reduced Risk of Poststroke Pneumonia in Thrombolyzed Stroke Patients with Continued Statin Treatment. *Int. J. Stroke* 10 (1), 61–66. doi:10.1111/j.1747-4949.2012.00864.x

Scicali, R., Di Pino, A., Ferrara, V., Urbano, F., Piro, S., Rabuazzo, A. M., et al. (2018). New Treatment Options for Lipid-Lowering Therapy in Subjects with Type 2 Diabetes. *Acta Diabetol.* 55 (3), 209–218. doi:10.1007/s00592-017-1089-4

Tziomalos, K., Athyros, V. G., Karagiannis, A., and Mikhailidis, D. P. (2009). Dyslipidemia as a Risk Factor for Ischemic Stroke. *Curr. Top. Med. Chem.* 9 (14), 1291–1297. doi:10.2174/156802609789869628

Wang, K. W., Feng, C., Wu, Y. F., Huang, J., Xiao, W. B., and Xia, S. D. (2020). Statin Pretreatment Might Be Associated with Decreased Myocardial Injury after Ischemic Stroke. *J. Stroke Cerebrovasc. Dis.* 29 (5), 104697. doi:10.1016/j.jstrokecerebrovasdis.2020.104697

Wei, L., Wang, J., Thompson, P., Wong, S., Struthers, A. D., and MacDonald, T. M. (2002). Adherence to Statin Treatment and Readmission of Patients after Myocardial Infarction: a Six Year Follow up Study. *Heart* 88 (3), 229–233. doi:10.1136/heart.88.3.229

WHO (2020). Defined Daily Dose (DDD). [cited 2020 Sep 1]; Available from.https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/

Yeramaneni, S., Kleindorfer, D. O., Sucharew, H., Alwell, K., Moomaw, C. J., Flaherty, M. L., et al. (2017). Hyperlipidemia Is Associated with Lower Risk of Poststroke Mortality Independent of Statin Use: A Population-Based Study. *Int. J. Stroke* 12 (2), 152–160. doi:10.1177/1747493016670175

Yousufuddin, M., and Young, N. (2019). Aging and Ischemic Stroke. *Aging (Albany NY)* 11 (9), 2542–2544. doi:10.18632/aging.101931

Zhao, J., Zhang, X., Dong, L., Wen, Y., and Cui, L. (2014). The many Roles of Statins in Ischemic Stroke. *Curr. Neuropharmacol* 12 (6), 564–574. doi:10.2174/1570159X12666140923210929

Zhu, J., Ma, M., Fang, J., Bao, J., Dong, S., Chen, N., et al. (2020). Prestroke Statin Use Enhances Collateralization in Acute Ischemic Stroke Patients. *Restor Neurol. Neurosci.* 38 (4), 311–321. doi:10.3233/RNN-201012

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Big Data and Real-World Data based Cost-Effectiveness Studies and Decision-making Models: A Systematic Review and Analysis

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Background: Big data and real-world data (RWD) have been increasingly used to measure the effectiveness and costs in cost-effectiveness analysis (CEA). However, the characteristics and methodologies of CEA based on big data and RWD remain unknown. The objectives of this study were to review the characteristics and methodologies of the CEA studies based on big data and RWD and to compare the characteristics and methodologies between the CEA studies with or without decision-analytic models.
Methods: The literature search was conducted in Medline (Pubmed), Embase, Web of Science, and Cochrane Library (as of June 2020). Full CEA studies with an incremental analysis that used big data and RWD for both effectiveness and costs written in English were included. There were no restrictions regarding publication date.
Results: 70 studies on CEA using RWD (37 with decision-analytic models and 33 without) were included. The majority of the studies were published between 2011 and 2020, and the number of CEA based on RWD has been increasing over the years. Few CEA studies used big data. Pharmacological interventions were the most frequently studied intervention, and they were more frequently evaluated by the studies without decision-analytic models, while those with the model focused on treatment regimen. Compared to CEA studies using decision-analytic models, both effectiveness and costs of those using the model were more likely to be obtained from literature review. All the studies using decision-analytic models included sensitivity analyses, while four studies no using the model neither used sensitivity analysis nor controlled for confounders.
Conclusion: The review shows that RWD has been increasingly applied in conducting the cost-effectiveness analysis. However, few CEA studies are based on big data. In future CEA studies using big data and RWD, it is encouraged to control confounders and to discount in long-term research when decision-analytic models are not used.

Keywords: big data, real-world data, cost-effectiveness analysis, pharmacoeconomics, systematic review

BACKGROUND

With the development of health care technologies, a large number of innovative medications and health-related interventions have been approved and available on the market (Claxton et al., 2011; Hughes-Wilson et al., 2012). While these new therapies deliver better health outcomes, they often come with additional economic burdens (Hughes-Wilson et al., 2012). The cost-effectiveness analysis (CEA) is one of the economic evaluation techniques comparing both outcomes and costs between two or more interventions, which could help decision-makers to decide the most appropriate intervention and help payers to estimate the economic burden (Eichler et al., 2004; Drummond and McGuire, 2005; Bowrin et al., 2019). When the effectiveness is measured by a utility, it is called cost-utility analysis (CUA) (Drummond and McGuire, 2005). CEA has been increasingly used by health technology assessment (HTA) agencies in many countries for the decision-making of health-related interventions, including but not limited to market access, pricing, and formulary (Yang et al., 2008; Clement et al., 2009; Ciani and Jommi, 2014; Dakin et al., 2015; Jönsson, 2015).

CEA can be directly performed based on randomized controlled trials (RCTs) or pragmatic studies, or it can be indirectly conducted using decision-analytic models with mixed data derived from RCTs and the real-world settings (Drummond and McGuire, 2005; Briggs et al., 2006). Decision-analytic models, such as the decision tree and the Markov model, are a systematic decision-making approach widely using in the economic evaluation of healthcare interventions to compare decisions under uncertainty (Drummond and McGuire, 2005; Briggs et al., 2006). Real-world data (RWD) provided by observational studies other sources, including medical claims data and electronic health records (EHRs) have been used more and more in CEA studies (Drummond, 1996; Terkola et al., 2017; Bowrin et al., 2019). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real-World Data Task Force published a report supporting the use of RWD for coverage and payment decisions in 2007, which defined RWD as the data used not collected in conventional RCTs (Garrison et al., 2007). Specifically, six sources of RWD were defined by the ISPOR, including supplements to traditional RCTs, large simple trials, registries, administrative data, health surveys, and EHRs and medical chart reviews. In 2017, ISPOR and International Society for Pharmacoepidemiology (ISPE) Joint Task Force published an article about the practice for real-world studies of comparative effectiveness (Berger et al., 2017). Compared to the RCTs considered as the "golden standard" in evaluating efficacies, RWD from observational studies or other real-world settings features a larger sample size (Silverman, 2009; Makady et al., 2018). Additionally, real-world settings can offer long-term scrutinization of effectiveness, which is reliable and ensures less uncertainty in a lifetime decision-analytic model compared to the RCTs commonly designed with a relatively short time horizon (Makady et al., 2018; Bowrin et al., 2019).

With the evolvement of technology, big data have been used more and more often in health care settings. Big data are a special kind of real-world data, which are characterized by high volume, high velocity, high variety, high value, and high veracity (5Vs) (Mehta and Pandit, 2018). Big data combine data from a variety of sources, including insurance claims, electronic medical records, patient-reported data, social media, etc. The combined data can be analyzed to predict the diagnosis and medication administration patterns using artificial intelligence models such as machine learning to compare health-related interventions (Wordsworth et al., 2018). However, because many big data are unstructured, certain challenges in the data collection, management, cleaning, and analysis need to be addressed before big data can be widely used in CEA studies (Wordsworth et al., 2018).

Limited studies have systematically reviewed the characteristics, methodologies, and quality of CEA studies based on big data and RWD. A study in 2019 reviewed the limitations in using RWD for CEA studies (Mehta and Pandit, 2018). However, this review does not include specific CEA studies using RWD, but overview literature (Mehta and Pandit, 2018). In addition, no studies have examined the differences between CEA studies based on big data and RWD with or without decision-analytic models. To fill the gap in the literature, the objectives of this study were to review the characteristics and methodologies of the cost-effectiveness analysis based on big data and real-world data and to compare the characteristics and methodologies between the cost-effectiveness analyses with or without decision-analytic models.

METHODS

Search Strategy and Sources

A comprehensive literature search was implemented to identify CEA studies using big data and RWD. The literature search was conducted within the scope of four databases (as of June 2020) including Medline (Pubmed), Embase, Web of Science, and Cochrane Library. In addition, manual searches on the reference lists of included studies as well as related systematic reviews were performed to ensure the retrieval completeness. Search terms used in this study include cost-effectiveness analysis, cost-utility analysis, economic evaluation, pharmacoeconomics, big data, real-world study, real-world evidence, real-world data, RWD, RWE, RWS, electronic health records, EHRs, claims, and registry. Details are shown in **Supplemental Material S1**.

Eligibility Criteria

Full CEA studies with an incremental analysis that compared both incremental effectiveness and incremental cost between two or more interventions that used big data and RWD for both effectiveness and costs written in English were included. The definition of RWD in this review was based on the report published by ISPOR, where RWD was defined as data not derived from RCTs but rather come from pragmatic trials, registries, administrative data, health surveys, electronic records, or paper medical charts (Garrison et al., 2007). Big data were identified if two or more RWD were combined in a

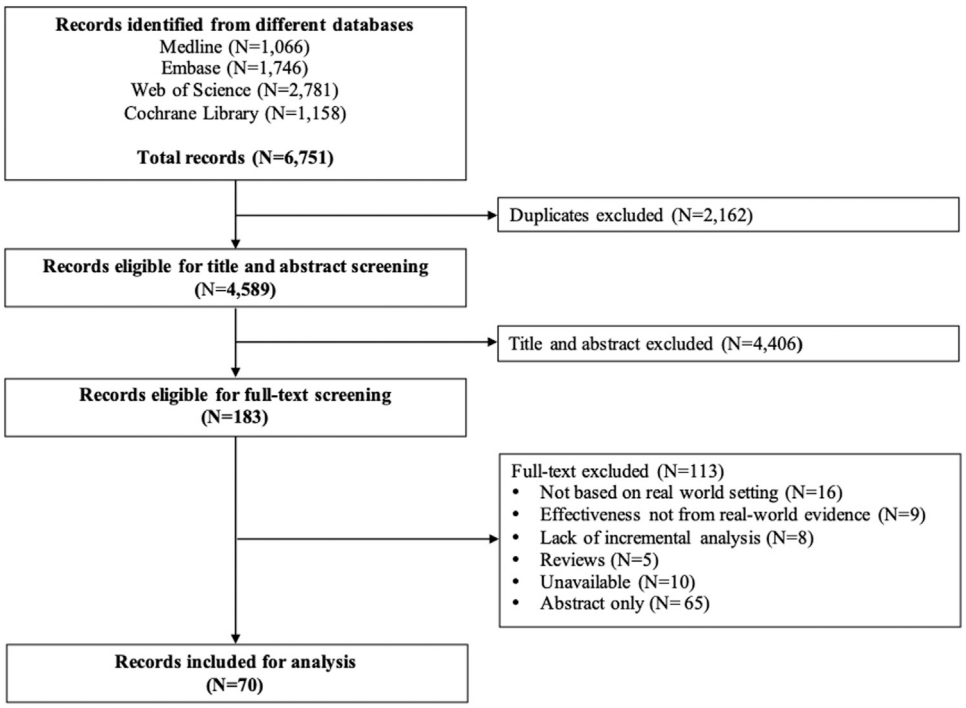

FIGURE 1 | Flowchart of publication selection.

single parameter, or if any artificial intelligent methods, such as machine learning and deep learning methods, were used to process the data (Mehta and Pandit, 2018; Wordsworth et al., 2018). Furthermore, there were no restrictions regarding the publication date. Cost-minimization analysis, cost-of-illness, cost-benefit analysis, reviews, meta-analysis, comments, letters, protocols, posters or presentations at conferences or workshops, literature unavailable, and studies that are not health-related were excluded.

Study Selection

According to the patient/population, intervention, comparison and outcomes (PICOS) principle, patients were any patients, data for intervention and control groups were from the real world, and outcomes were ICER (Amir-Behghadami and Janati, 2020). Two rounds of screening were carried out independently by two reviewers after removing duplicates. In case a disagreement was expressed, a senior reviewer made the final decision. In the first round, titles and abstracts were screened for eligibility. Studies were included if 1) baseline population is based on real-world studies; 2) big data and RWD are used for both effectiveness and costs; 3) transition probabilities in the decision-analytic models are not obtained from RCTs. Then, the full-text review was performed for verification of potentially eligible studies according to the eligibility criteria. The entire selection process, including study identification, eligibility screening, and selection of full-text articles, followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009).

Information Extraction and Data Synthesis

The extracted information included the study characteristics: title, name of the first author, published year, study regions, affiliations of the first author, funding sources, diseases, interventions, and sample size. We also collected information on the study methodologies: study design, data type (RWD or big data), time horizon, methods of controlling confounders, the primary outcome, indirect costs (including the cost of absence from paid work, reduced productivity at paid work, and unpaid production), sources of effectiveness, sources of costs, report of missing data, methods of handling missing data, threshold consideration, sensitivity analysis, and discount rate (Liljas, 1998; McNamee, 2005). The process of study selection, along with the included and excluded number of studies, was presented in a PRISMA flowchart (**Figure 1**). The descriptive characteristics and methodologies were summarized and compared between the cost-effectiveness analyses with or without decision-analytic models.

Quality Assessment

We assessed the quality of the included studies using the Quality of Health Economic Studies (QHES) instrument (Ofman et al., 2003; Di Marco et al., 2018; McQueen et al., 2018). The QHES instrument consists of 16 items with scores ranging from 1 to 9, and the total score of the instrument is 100. During the assessment process, if the included study satisfied the criterion of an item, the study received an item-specific score, otherwise it received a score of zero. The quality assessment was conducted by two reviewers independently, and any controversies were resolved by discussion with a third investigator to reach a

consensus. The QHES has a score-based grading system. The QHES has a score-based grading system. The scores are grouped into four groups: extremely poor quality (0–24), poor quality (25–49), fair quality (50–74), and high quality (75–100) (Ofman et al., 2003). Details of the QHES instrument are shown in **Supplemental Material S2**.

RESULTS

Overview

The systematic literature search identified 6,751 studies after applying search strategies from different databases combined. After removing duplicates, 4,589 studies were eligible for the title and abstract screening. Upon screening of the titles and abstracts, 4,406 studies were excluded. The full-text screening was conducted on 183 eligible studies. A total of 113 studies were excluded from the full-text review, and a total of 70 studies were finally included for review (**Figure 1**). The number of publications on CEA studies based on big data and RWD increased over the years, and the majority of the studies were published between 2011 and 2020 (**Figure 2**).

Charcteristics of Included Studies

Among 70 studies included, 37 (52.9%) were based on decision-analytic models, and 33 (47.1%) were not. The study regions of most studies were in Europe (42.9%). For the research design, the number of studies using CEA (55.7%) was slightly more than that of those using CUA (44.3%). Nearly 70% of the studies had a sample size higher than 100, and around a quarter of the stuides did not report the sample size. The most frequently used study perspective was the health care system (45.7%), followed by society (22.9%) and patients (11.4%). Most of the authors were from government or academic institutions (67.1%), and most of the funding came from the industry (48.6%). Neoplasms (25.7%) and circulation diseases (24.3%) were the most frequently studied diseases. The most frequently evaluated intervention was pharmacological treatment (54.3%). (**Table 1**).

Methodologies of Included Studies

The majority of included studies (65.7%) reported patient baseline information. Nearly half of the studies (48.6%) did not report methods used to control for confounders, and matching (30.0%) was the most frequently used method for controlling, followed by regression (17.1%). Quality-adjusted life year (QALY) was the most frequently used effectiveness measure (55.7%), followed by the clinical endpoint (21.4%) and life year (18.6%). One-fifth of the studies included both direct and indirect costs (21.4%). The main sources of effectiveness were observational studies (48.6%), followed by registry and hospital information system (22.9%), while the main sources of cost were claims (31.4%), followed by the hospital information system (22.9%), and governmental published sources (18.6%). More than 70% of the studies did not report missing data of RWD. Among the studies with the report of missing data, excluding individuals with missing data was the most common method of handling the missing data, followed by imputation (25.0%). In addition, one study (5.0%) requested missing data from additional sources, while three studies reported missing data but did not use any method for handling. Half of the studies (52.9%) used a threshold to determine cost-effectiveness, and nearly one-third of the studies (17.1%) did not report any sensitivity analyses. The majority of the studies (82.9%) used a time horizon longer than 1 year, and nearly one-fifth of the studies (17.1%) did not report the time horizon. The number of discounted (52.9%) and undiscounted (47.1%) studies was about the same. (**Table 2**).

Comparison of Studies With or Without Decision-Analytic Models

The majority of included studies with decision-analytic models used CUA (86.5%), while most of the studies without the model used CEA (78.8%). (**Table 1**). For the diseases evaluated in the studies, **Figure 3** showed that Studies with decision analysis models were more likely to study on pharmacological interventions, management programs, and screening, while studies not based on decision analysis models were more likely to study on surgical interventions, treatment regimens, and devices. In terms of the interventions evaluated, **Figure 4** illustrated that the studies with decision-analytic models preferred to evaluate pharmacological interventions, management programs, and screening, whereas those without models preferred to study surgical interventions, treatment regimens, and devices.

Compared to the studies without decision-analytic models, those with the model were less likely to control for confounding variables and preferred to use QALYs as the effectiveness measure. However, the studies without the model were less likely to use threshold and sensitivity analysis, and the time horizon of them was shorter compared to the studies with the model. For sources of effectiveness, compared to the studies without decision-analytic models, the effectiveness of those with the model was less likely to be obtained from claims and health information systems and was more likely to be obtained from the registry and observational studies (**Figure 5**). As for sources of costs, **Figure 6** demonstrated that official resources, registry, observational studies, and especially literature review were preferable for the studies using decision-analytic models, while claims and hospital information systems were preferable for those not using the models. In terms of missing data, the studies that did not use the model were more likely to report missing data. The methods of handling missing data were mainly excluding regardless of whether the model was used.

Quality of Included Studies

The average QHES score for the studies with decision-analytic models was 95.7, while the score for the studies without the model was 88.7. The detailed results of the quality assessment are shown in **Figure 7**. Most of the included studies were conducted reasonably well. However, many studies have failed to deal with the time horizon, where only 51.4% of studies stated the time horizon and used discounting correctly.

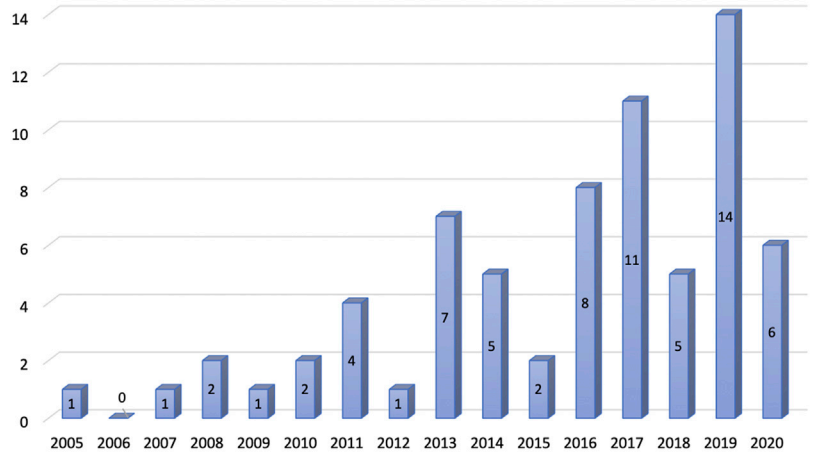

FIGURE 2 | Trends in the publications of real-world based cost-effectiveness analysis.

DISCUSSION

This systematic literature review assessed the characteristics and methodologies of the CEA studies based on big data and RWD. Out of 70 included studies, we found that the number of the CEA studies based on big data and RWD has been increased over the years, and the majority of the studies were published between 2011 and 2020, which is similar to previous studies reviewing the economic evaluations based on RWD and routine data (Gansen, 2018; Parody-Rúa et al., 2020). We also found that the study region with the most stuides was Europe. This distribution is as expected given that many European countries have HTA agencies and have been using CEA studies to make reimbursement and formulary decisions (Dakin et al., 2015; Makady et al., 2018). Most of the first authors were from government or academic institutions, and most of the funding came from the industry, which is similar to a previous study (Parody-Rúa et al., 2020).

A study by Bowrin et al. systematically reviewed the barriers of using RWD in CEA modeling as well as the existing guidelines and recommendations for incorporating RWD in CEA modeling, in which they found that RWD is valuable in CEA studies for their internal information and suggested that the methods and potential applications of RWD in CEA should be studied (Bowrin et al., 2019). Our study complemented this research gap with a systematic review of the published CEA studies based on big data and RWD. Bowrin et al. indicated that there might be several barriers in the CEA studies using RWD, among which confounding bias was one of the main issues (Bowrin et al., 2019). Our findings are consistent with their results. In the 70 studies using RWD we included, we found that nearly half of the RWD-based studies lacked the control for confounders. Direct use of RWD may be biased due to possible differences in characteristics between the control and experimental groups and may result in causality not being explained. Confounders need to be tightly controlled in future studies using RWD. In future research, it is important to control for confounders and make the experimental group and the control group comparable. A similar issue is a lack of reporting baseline information of the study population. If there is a deviation between RWD and the baseline characteristics of the study population in the CEA, the direct use of the RWD data may be biased. The studies that did not report baseline information accounted for nearly of the studies that used the decision-analytic model. Although all of these studies used sensitivity analysis that could reduce the uncertainty, the reporting of the results of base case analysis might be biased. Bowrin et al. also mentioned that CEA using RWE might have the issue of missing data (Bowrin et al., 2019). During our review, we found that more than 70% of the included studies did not report missing data and how it was handled. This issue was more common in the CEA studies using the model. In future research, missing data should be strictly reported for CEA studies using RWD. Although Bowrin et al. indicated that the use of RWD might have a small sample size, in our review (Bowrin et al., 2019), we found that most the included studies had a sample size larger than 500, and even eight studies had a sample size of more than 10,000. However, there were more than a quarter of the included studies without reporting the sample size.

Compared with the previous study, we also compared the CEA study using RWD with and without the decision-analytic model. The CEA studies using models were more likely to study chronic diseases and to use a lifetime horizon, which might be due to the ability of decision-analytic models in simulating the lifetime cost-effectiveness (Drummond and McGuire, 2005; Tarride et al., 2010). Although CEA studies directly based on RWD can also provide long-term effectiveness and costs, they are rarely lifelong. However, in most of the studies using the model with a lifetime horizon, RWD-based effectiveness did not reach the lifetime. Although sensitivity analysis can partially solve this problem by reducing the uncertainty with a range of ICER, how to solve the potential problems of extrapolating the use of RWD still needs to be studied (Makady et al., 2018). In terms of the diseases studied, the studies without decision-analytic were more likely to study pharmacological interventions, while those with the model were more likely to focus on the treatment regimen. A direct comparison of pharmacological interventions without the model can reduce the uncertainty introduced by the model

TABLE 1 | Characteristics of included studies.

Characteristics	Total *N* = 70		Analytic decision model *N* = 37		Non-analytic decision model *N* = 33	
	N	%	*N*	%	*N*	%
Year						
2000–2010	7	10.0	4	10.8	3	9.1
2011–2015	19	27.1	11	29.7	8	24.2
2016–2020	44	62.9	22	59.5	22	66.7
Study regions						
Africa	2	2.9	0	0.0	2	6.1
Asia	18	25.7	11	29.7	7	21.2
Europe	30	42.9	18	48.6	12	36.4
Oceania	2	2.9	2	5.4	0	0.0
North America	18	25.7	6	16.2	12	36.4
Study types						
CEA	31	44.3	5	13.5	26	78.8
CUA	39	55.7	32	86.5	7	21.2
Sample size						
0–100	4	5.7	0	0.0	4	12.1
101–500	18	25.7	10	27.0	8	24.2
501–1,000	9	12.9	5	13.5	4	12.1
1,001–10,000	13	18.6	4	10.8	9	27.3
≥10,001	8	11.4	2	5.4	6	18.2
NA	18	25.7	16	43.2	2	6.1
Cost perspectives						
Patients	8	11.4	3	8.1	5	15.2
Society	16	22.9	11	29.7	5	15.2
Health care system	32	45.7	17	45.9	15	45.5
Third-party payer	4	5.7	2	5.4	2	6.1
Others	3	4.3	2	5.4	1	3.0
NA	7	10.0	2	5.4	5	15.2
Affiliations of the first author						
Government/academia	47	67.1	26	70.3	21	63.6
Hospital	12	17.1	3	8.1	9	27.3
Industry	2	2.9	1	2.7	1	3.0
Consulting firms	9	12.9	7	18.9	2	6.1
Funding sources						
Government/academia	22	31.4	9	24.3	13	39.4
Industry	34	48.6	21	56.8	13	39.4
No funding	6	8.6	4	10.8	2	6.1
NA	8	11.4	3	8.1	5	15.2
Disease categories (Based on ICD-10 categories)						
I Certain infectious and parasitic diseases	4	5.7	2	5.4	2	6.1
II Neoplasms	18	25.7	7	18.9	11	33.3
IV Endocrine, nutritional and metabolic diseases	5	7.1	4	10.8	1	3.0
V Mental and behavioral disorders	3	4.3	0	0.0	3	9.1
IX Diseases of the circulatory system	17	24.3	8	21.6	9	27.3
X Diseases of the respiratory system	6	8.6	2	5.4	4	12.1
XIII Diseases of the musculoskeletal system and connective tissue	7	10.0	6	16.2	1	3.0
Others	1	1.4	1	2.7	0	0.0
NA	4	5.7	3	8.1	1	3.0
Intervention categories						
Pharmacological	38	54.3	25	67.6	13	39.4
Surgical	7	10.0	2	5.4	5	15.2
Treatment regimen	13	18.6	3	8.1	10	30.3
Management program	3	4.3	3	8.1	0	0.0
Prevention program	6	8.6	3	8.1	3	9.1
Screening	1	1.4	1	2.7	0	0.0
Devices	2	2.9	0	0.0	2	6.1

CEA: Cost-Effectiveness Analysis; CUA, Cost-Utility Analysis; NA, Not Available; ICD-10, International Classification of Diseases, 10th Revision.

TABLE 2 | The methodologies used of included studies.

Methodologies	Total*N* = 70		Analytic decision model*N* = 37		Non-analytic decision model*N* = 33	
	N	% (SD)	*N*	% (SD)	*N*	% (SD)
Patient baseline information						
Yes	46	65.7	19	51.4	27	81.8
No	24	34.3	18	48.6	6	18.2
Confounders controlled						
Randomization	3	4.3	1	2.7	2	6.1
Matching	21	30.0	8	21.6	13	39.4
Regression	12	17.1	1	2.7	11	33.3
NA	34	48.6	27	73.0	7	21.2
Analytic models						
Decision tree	4	10.8	4	10.8	-	-
Markov	30	81.1	30	81.1	-	-
Others	3	8.1	3	8.1	-	-
Effectiveness						
QALYs	39	55.7	30	81.1	9	27.3
DALYs	1	1.4	0	0.0	1	3.0
Life years	13	18.6	5	13.5	8	24.2
Clinical endpoint	15	21.4	2	5.4	13	39.4
Health care utilization	2	2.9	0	0.0	2	6.1
Cost input						
Only direct costs	55	78.6	27	73.0	28	84.8
Both direct and indirect costs	15	21.4	10	27.0	5	15.2
Sources of effectiveness						
Claims	16	22.9	10	27.0	6	18.2
Registry	9	12.9	2	5.4	7	21.2
Observational studies	11	15.7	2	5.4	9	27.3
Hospital information system	34	48.6	23	62.2	11	33.3
Sources of costs						
Claims	13	18.6	8	21.6	5	15.2
Registry	10	14.3	6	16.2	4	12.1
Literature review	22	31.4	9	24.3	13	39.4
Government-published resources	16	22.9	7	18.9	9	27.3
Observational studies	2	2.9	1	2.7	1	3.0
Hospital information system	7	10.0	6	16.2	1	3.0
Report of missing data						
Yes	20	28.6	6	16.2	14	42.4
No	50	71.4	31	83.8	19	57.6
Methods of handling missing data[a]						
Imputation	5	25.0	0	0.0	5	35.7
Excluding	11	55.0	3	50.0	8	57.1
Request from other sources	1	5.0	1	16.7	0	0.0
No	3	15.0	2	33.3	1	7.1
ICER Threshold						
Yes	37	52.9	27	73.0	10	30.3
No	33	47.1	10	27.0	23	69.7
Sensitivity analysis						
Only deterministic sensitivity analysis	15	21.4	7	18.9	8	24.2
Only probabilistic sensitivity analysis	20	28.6	12	32.4	8	24.2
Both deterministic and probabilistic sensitivity analysis	23	32.9	18	48.6	5	15.2
NA	12	17.1	0	0.0	12	36.4
Time horizon						
≤ 1 year	12	17.1	6	16.2	6	18.2
> 1 year	21	30.0	6	16.2	15	45.5
Lifetime	25	35.7	22	59.5	3	9.1
NA	12	17.1	3	8.1	9	27.3
Discount rate						
Yes	37	52.9	30	81.1	7	21.2
No	33	47.1	7	18.9	26	78.8
QHES score	92.4	7.0	95.7	5.4	88.7	6.8

NA, Not Available; QALY, Quality-Adjusted Life Year; DALY, Disability-Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio; QHES, Quality of Health Economic Studies.
[a]*The denominator is the 20 of studies with report of missing data.*

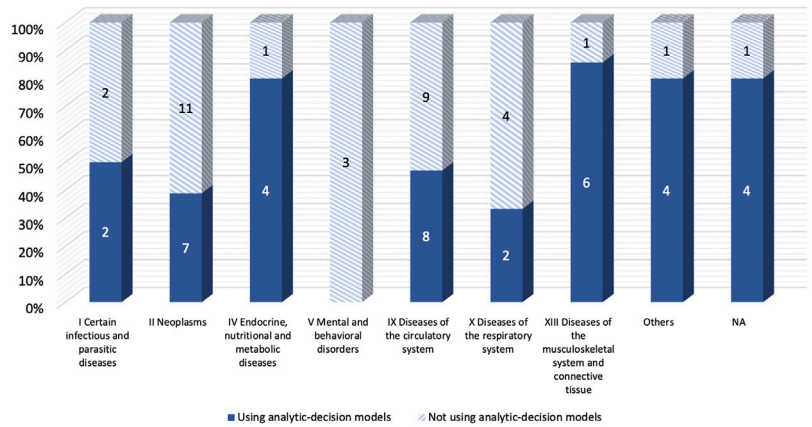

FIGURE 3 | Differences in disease categories between real-world cost-effectiveness analysis with or without decision-analytic model.

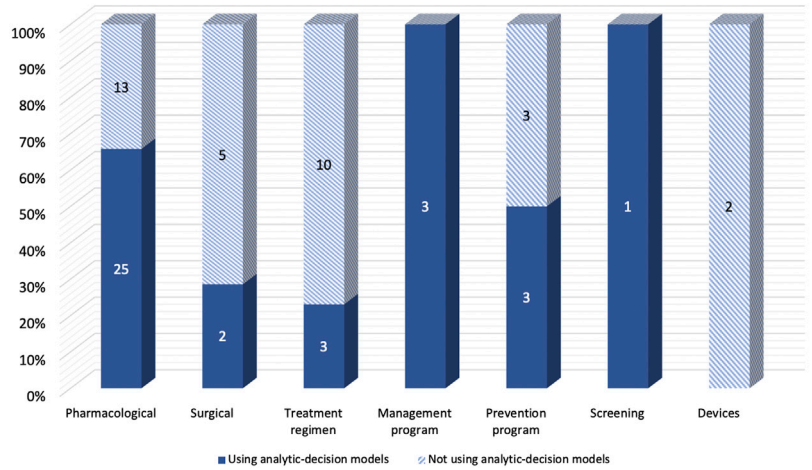

FIGURE 4 | Differences in intervention categories between real-world cost-effectiveness analysis with or without decision-analytic model.

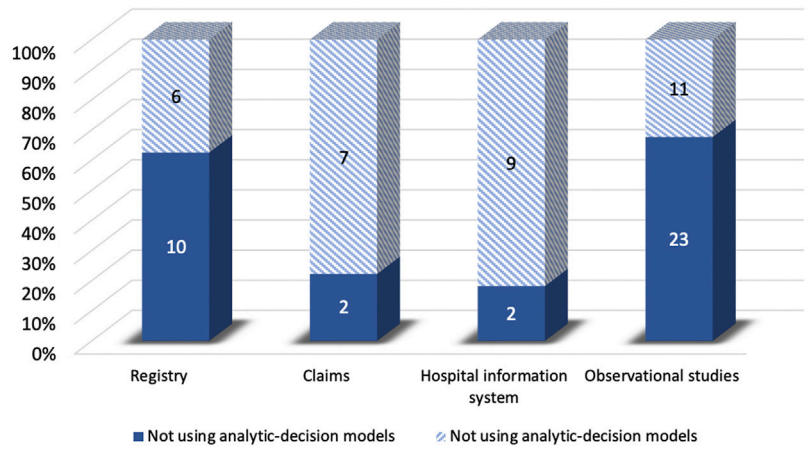

FIGURE 5 | Differences in effectiveness sources between real-world cost-effectiveness analysis with or without decision-analytic model.

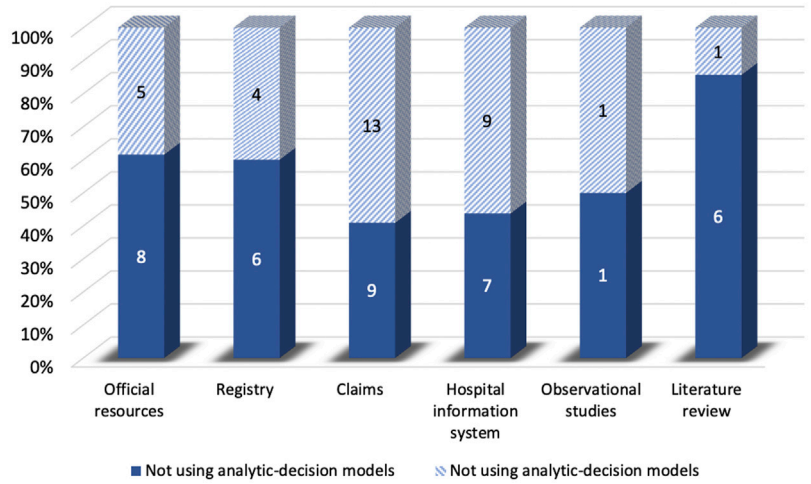

FIGURE 6 | Differences in cost sources between real-world cost-effectiveness analysis with or without decision-analytic model.

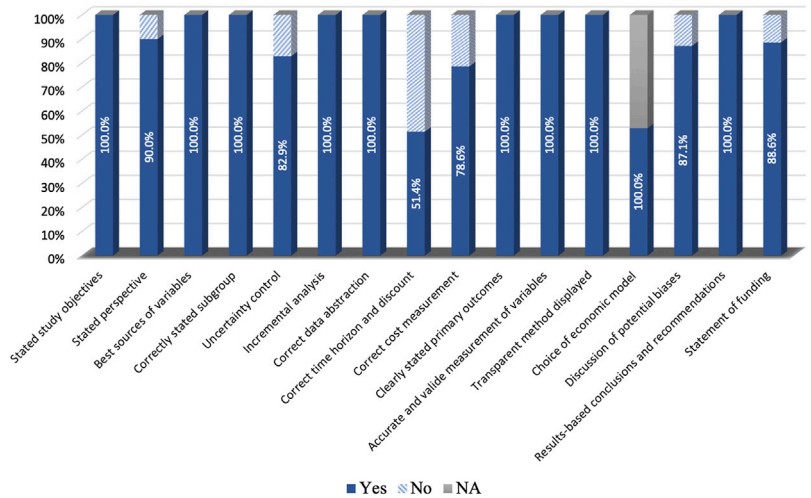

FIGURE 7 | Quality assessment for the included studies.

(Briggs, 2000). However, for the treatment regimen, it might be difficult to select a sample in a real-world setting where the treatment regimen is always complicated (Schulman et al., 2013). Consequently, those studies aiming to compare different treatment regimens preferred to use a model approach that allows greater freedom in the choice of study and control groups (Behar et al., 2017; Thronicke et al., 2020). This might be due to the fact that most of the studies with the model used sensitivity analysis to control for uncertainty. Compared to CEA studies with decision-analytic models, both the effectiveness and costs were more likely to be obtained from the literature review, which might be due to CEA studies using models often use mixed data from different sources (Briggs et al., 2006). In addition, the effectiveness of the studies using the decision-analytic model was mainly from claims and hospital information system, while the sources of studies without the model were more extensive. In addition to the above two, registry and observational studies were also main sources for studies without the model. We also found that four studies without models did not test the uncertainty of the study or control for confounders for assessing the effectiveness and costs (Olivares et al., 2008; Isla-Tejera et al., 2013; Tsai et al., 2018; Chan et al., 2020). As we discussed above, the lack of these methods could bring biases to results, and it is difficult to inform decision-making by deterministic results alone (Briggs, 2000; Parody-Rúa et al., 2020). Furthermore, in long-term CEA studies without the model, most of them were not discounted. Some of these studies even used a life-long time horizon (Liao et al., 2017; Wei et al., 2017). Without the discounting for the long-term of effectiveness and costs might overestimate the cumulative effectiveness and costs and might

bias in ICER depends on a greater impact of the discounting on costs or effectiveness (Gravelle and Smith, 2001). In addition, we used the QHES to identify the quality of the included studies. Compared to the CHEERS, the QHES items have a better specificity, and QHES has a scoring system, which could facilitate the comparison of different studies (Ofman et al., 2003; Husereau et al., 2013). We found that the score of the studies included was higher than 75 regardless of whether the model was used or not, indicating a high quality of the studies.

In addition to the specific issues of using RWD, we also found some common problems related to CEA in the included research. The vast majority of CEA studies that adopted a social perspective included indirect costs. However, there were still several studies from a societal perspective that did not include indirect costs (Aarnio et al., 2015; van Leent et al., 2015; Dor et al., 2018; de Jong et al., 2019a; de Jong et al., 2019b; Voermans et al., 2019). Although none of these studies focusing on malignant diseases that can cause serious damage to the patient's productivity or infectious diseases that can infect others (Aarnio et al., 2015; van Leent et al., 2015; Dor et al., 2018; de Jong et al., 2019a; de Jong et al., 2019b; Voermans et al., 2019), ignoring indirect costs to some extent underestimates the total costs and the benefits of productivity that could accrue to patients from more effective interventions (Drummond and McGuire, 2005). When using society as a research perspective of cost, opportunity cost instead of acquisition cost should be measured as the cost of interventions or programs. However, in all the studies that we included using society as the perspective, the costs were directly used acquisition costs, and there was no discussion why these costs were not adjusted into opportunity costs (Lindgren et al., 2009; Lekander et al., 2010; Yang et al., 2010; Lekander et al., 2013; Aarnio et al., 2015; Zhao et al., 2016; Tanaka et al., 2017; Vassall et al., 2017; Dor et al., 2018; de Jong et al., 2019a; de Jong et al., 2019b; Behan et al., 2019; Lin et al., 2019; Voermans et al., 2019; Wang et al., 2019; Arrobas et al., 2021). This might lead to the overestimation of costs and ICER. In addition, we found that most of the utilities used in the studies using decision-analytic models were derived from literature review, which might not suit the model population and result in potential biases. Although this limitation is widespread in research using decision-analytic models and not only limited to those studies using RWD, such a limitation should also be circumvented in order to improve the validity of the study.

However, in this study we found that less big data is used in CEA. When searching for literature, in order to avoid the inclusion of the studies only using RWD as one minor part of the data sources, we used a more rigorous search strategy. This might lead to a reduction in the scope of our included studies and might excluded some CEA studies that used big data. However, because many studies might have multiple data sources, especially the CEA studies using the decision-analytic model. Including all the studies where RWD were used might lead to too much literature and reduce the feasibility of the study. Given the potentials of big data, we encourage future CEA studies to use big data to support decision-making (Wordsworth et al., 2018). Big data are featured by high volume, high velocity, high variety, high value, and high veracity (Mehta and Pandit, 2018). Beyond the economic evaluation of diseases or interventions based on a cohort, big data can act as an important role in personalized precision health economics and outcomes research (p-HEOR) (Chen et al., 2020). Advanced predictive algorithms of applying big data such as natural language processing (NLP) and machine learning (ML) should be used more in CEA studies and other economic evaluations (Fahr et al., 2019). Given the potentials of big data, we encourage future CEA studies to use big data to support decision-making.

According to the trend in the publications, the number of CEA studies using RWD is likely to continue increasing over the next decades. The 21st Century Cures Act passed in 2016 emphasized the use of RWD to support regulatory decision making, including the approval of new indications for approved drugs, and a series of guidance was launched later (Hudson and Collins, 2017). It is not difficult to imagine that over the next decades, more and more CEA studies will use RWD. In the case of big data, over the next decades, relevant CEA research using big data is likely to emerge, but not on a large scale, given that few mature algorithms and related methods are available (Fahr et al., 2019). Big data have far-reaching potential for prediction and could be used in some long-term CEA studies to replace some of the current methods to predict long-term effectiveness and costs (Fahr et al., 2019; Chen et al., 2020).

Although there is no systematic guideline on the use of RWE in CEA, there is some guidelines about using RWD from certain sources. Deidda et al. published a framework on the use of natural experiments, and some of the items contained therein are similar to the problems we found, which might be helpful to guide future CEA research using natural experiments as RWD sources to avoid methodology problems (Deidda et al., 2019). However, considering that there are more and more researches using RWD, there is still a need for systematic guidance on using RWD.

Some study limitations are worth mentioning. First, although the searching strategies used various terms, only a restricted set of synonyms was utilized within the systematic search. However, the terms used in the searching strategies are comparable to other reviews regarding the cost-effectiveness analysis. Second, since many diseases, as well as interventions, were included in the study, we did not compare the result of CEA studies based on big data and RWD to that of CEA studies based on RCT, because there were too much CEA literature using RCT data or mixed data for each disease or intervention, and it was difficult to ensure that all the literature can be fully included, for which the results of comparing might be biased. In future research, it is needed to conduct systematic reviews comparing the result of CEA studies based on big data and RWD to that of CEA studies based on RCT for a specific disease or intervention, in which the published literature can be covered completely. Third, the searching terms were restricted in the title, abstract, and keywords. Some studies based on big data and RWD but not mentioned in each respective field might have been missed. In addition, although our research found that there were eight studies with a sample size of more than 10,000, according to our definition of big data, these were not classified as studies using big data. When doing this research, there was no specific definition of big data in the HTA. Therefore, during the search process, we used definitions that if two or more RWD were combined in a single parameter, or if any artificial intelligent

methods were used to process the data, which might limit the economic evaluation that we can include on the use of big data to a certain extent. Future research specifically on big data is still needed to enrich the review of this type of research. Fourth, this study only focused on CEA studies, and did include CBA studies, because we were concerned that if CBA was included, there might be some differences from CEA when extracting methodology or results. Future studies are needed for CBA studies using RWD. Finally, only full-text studies in English were included in the review, resulting in the disqualification of published studies that met other inclusion criteria.

CONCLUSION

A total of 70 studies were identified in this systematic literature review regarding cost-effectiveness analysis based on big data and real-world data. The review shows that big data and RWD have been increasingly applied in conducting the cost-effectiveness analysis. However, few CEA studies are based on big data characterized by 5Vs. The characteristics and methodologies were described and compared between the studies with decision-analytic models as well as the ones without the model. In future CEA studies using big data and RWD, it is encouraged to control confounders and to discount in long-term research when decision-analytic models are not used.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Concept and design: ZKL, JY. Acquisition, analysis, and/or interpretation of data: ZKL, XX, JY, BJ. Drafting of the manuscript: ZKL, XX, TL, JY, BJ. Critical revision of the manuscript for important intellectual content: JW, JY, BJ. Statistical analysis: XX.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.700012/full#supplementary-material

REFERENCES

Aarnio, E., Korhonen, M. J., Huupponen, R., and Martikainen, J. (2015). Cost-effectiveness of Statin Treatment for Primary Prevention in Conditions of Real-World Adherence-Eestimates from the Finnish Prescription Register. *Atherosclerosis* 239, 240–247. doi:10.1016/j.atherosclerosis.2014.12.059

Ademi, Z., Liew, D., Hollingsworth, B., Steg, P. G., Bhatt, D. L., and Reid, C. M. (2013). Is it Cost-Effective to Increase Aspirin Use in Outpatient Settings for Primary or Secondary Prevention? Simulation Data from the REACH Registry Australian Cohort. *Cardiovasc. Ther.* 31, 45–52. doi:10.1111/j.1755-5922.2011.00291.x

Ademi, Z., Reid, C. M., Hollingsworth, B., Stoelwinder, J., Steg, P. G., Bhatt, D. L., et al. (2011). Cost-effectiveness of Optimizing Use of Statins in Australia: Using Outpatient Data from the REACH Registry. *Clin. Ther.* 33, 1456–1465. doi:10.1016/j.clinthera.2011.08.004

Amir-Behghadami, M., and Janati, A. (2020). Population, Intervention, Comparison, Outcomes and Study (PICOS) Design as a Framework to Formulate Eligibility Criteria in Systematic Reviews. *Emerg. Med. J.* 37 (6), 387. doi:10.1136/emermed-2020-209567

Ariyaratne, T. V., Ademi, Z., Huq, M., Rosenfeldt, F., Duffy, S. J., Parkinson, B., et al. (2018). The Real-World Cost-Effectiveness of Coronary Artery Bypass Surgery versus Stenting in High-Risk Patients: Propensity Score-Matched Analysis of a Single-Centre Experience. *Appl. Health Econ. Health Pol.* 16, 661–674. doi:10.1007/s40258-018-0407-5

Arrobas, A., Barbosa, M. P., Rabiais, S., Vandewalle, B., and Félix, J. (2021). Cost-effectiveness of Omalizumab in Real World Uncontrolled Allergic Asthma Patients. *Pulmonology* 27, 124–133. doi:10.1016/j.pulmoe.2020.03.001

Barnett, P. G., Ignacio, R. V., Kim, H. M., Geraci, M. C., Essenmacher, C. A., Hall, S. V., et al. (2019). Cost-effectiveness of Real-World Administration of Tobacco Pharmacotherapy in the United States Veterans Health Administration. *Addiction* 114, 1436–1445. doi:10.1111/add.14621

Behan, C., Kennelly, B., Roche, E., Renwick, L., Masterson, S., Lyne, J., et al. (2019). Early Intervention in Psychosis: Health Economic Evaluation Using the Net Benefit Approach in a Real-World Setting. *Br. J. Psychiatry* 217, 484–490. doi:10.1192/bjp.2019.126

Behar, J. M., Chin, H. M., Fearn, S., Ormerod, J. O., Gamble, J., Foley, P. W., et al. (2017). Cost-Effectiveness Analysis of Quadripolar versus Bipolar Left Ventricular Leads for Cardiac Resynchronization Defibrillator Therapy in a Large, Multicenter UK Registry. *JACC Clin. Electrophysiol.* 3, 107–116. doi:10.1016/j.jacep.2016.04.009

Berger, M. L., Sox, H., Willke, R. J., Brixner, D. L., Eichler, H. G., Goettsch, W., et al. (2017). Good Practices for Real-World Data Studies of Treatment And/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Pharmacoepidemiol. Drug Saf.* 26, 1033–1039. doi:10.1002/pds.4297

Bowrin, K., Briere, J. B., Levy, P., Millier, A., Clay, E., and Toumi, M. (2019). Cost-effectiveness Analyses Using Real-World Data: an Overview of the Literature. *J. Med. Econ.* 22, 545–553. doi:10.1080/13696998.2019.1588737

Brennan, A., Bansback, N., Nixon, R., Madan, J., Harrison, M., Watson, K., et al. (2007). Modelling the Cost Effectiveness of TNF-Alpha Antagonists in the Management of Rheumatoid Arthritis: Results from the British Society for Rheumatology Biologics Registry. *Rheumatology (Oxford)* 46, 1345–1354. doi:10.1093/rheumatology/kem115

Briggs, A. H. (2000). Handling Uncertainty in Cost-Effectiveness Models. *Pharmacoeconomics* 17, 479–500. doi:10.2165/00019053-200017050-00006

Briggs, Andrew., Sculpher, Mark., and Claxton, Karl. (2006). *Decision Modelling for Health Economic Evaluation*. Oxford, UK: Oxford University Press.

Burn, E., Liddle, A. D., Hamilton, T. W., Judge, A., Pandit, H. G., Murray, D. W., et al. (2018). Cost-effectiveness of Unicompartmental Compared with Total Knee Replacement: a Population-Based Study Using Data from the National Joint Registry for England and Wales. *BMJ Open* 8, e020977. doi:10.1136/bmjopen-2017-020977

Cárdenas, M., de la Fuente, S., Font, P., Castro-Villegas, M., Romero-Gómez, M., Ruiz-Vílchez, D., et al. (2016). Real-world Cost-Effectiveness of Infliximab, Etanercept and Adalimumab in Rheumatoid Arthritis Patients: Results of the CREATE Registry. *Rheumatol. Int.* 36, 231–241. doi:10.1007/s00296-015-3374-2

Chan, C. L., Li, A. A., Chung, H. A., and Phan, D. V. (2020). Cost Effectiveness Analysis and Payment Policy Recommendation-Population-Based Survey with Big Data Methodology for Readmission Prevention of Patients with Paroxysmal Supraventricular Tachycardia Treated with Radiofrequency

Catheter Ablation. *Int. J. Environ. Res. Public Health* 17, 2334. doi:10.3390/ijerph17072334

Chen, G. F., Wei, L., Chen, J., Duan, Z. P., Dou, X. G., Xie, Q., et al. (2016). Will Sofosbuvir/Ledipasvir (Harvoni) Be Cost-Effective and Affordable for Chinese Patients Infected with Hepatitis C Virus? an Economic Analysis Using Real-World Data. *PLoS One* 11, e0155934. doi:10.1371/journal.pone.0155934

Chen, Y., Chirikov, V. V., Marston, X. L., Yang, J., Qiu, H., Xie, J., et al. (2020). Machine Learning for Precision Health Economics and Outcomes Research (P-HEOR): Conceptual Review of Applications and Next Steps. *J. Health Econ. Outcomes Res.* 7, 35–42. doi:10.36469/jheor.2020.12698

Cheng, H. M., Chiou, L. J., Chen, T. C., Sung, S. H., Chen, C. H., and Lang, H. C. (2019). Real-world Cost-Effectiveness of Drug-Eluting Stents vs. Bare-Metal Stents for Coronary Heart Disease-A Five-Year Follow-Up Study. *Health Policy* 123, 229–234. doi:10.1016/j.healthpol.2018.11.010

Chien, C. R., Hsia, T. C., and Chen, C. Y. (2014). Cost-effectiveness of Chemotherapy Combined with Thoracic Radiotherapy versus Chemotherapy Alone for Limited Stage Small Cell Lung Cancer: A Population-Based Propensity-Score Matched Analysis. *Thorac. Cancer* 5, 530–536. doi:10.1111/1759-7714.12125

Cho, J. H., Jang, H. M., Jung, H. Y., Choi, J. Y., Park, S. H., Kim, C. D., et al. (2018). A Real-World Cost-Effectiveness Analysis of Sevelamer versus Calcium Acetate in Korean Dialysis Patients. *Clin. Ther.* 40, 123–134. doi:10.1016/j.clinthera.2017.02.005

Ciani, O., and Jommi, C. (2014). The Role of Health Technology Assessment Bodies in Shaping Drug Development. *Drug Des. Devel Ther.* 8, 2273–2281. doi:10.2147/DDDT.S49935

Claxton, K., Paulden, M., Gravelle, H., Brouwer, W., and Culyer, A. J. (2011). Discounting and Decision Making in the Economic Evaluation of Health-Care Technologies. *Health Econ.* 20 (1), 2–15. doi:10.1002/hec.1612

Clement, F. M., Harris, A., Li, J. J., Yong, K., Lee, K. M., and Manns, B. J. (2009). Using Effectiveness and Cost-Effectiveness to Make Drug Coverage Decisions: a Comparison of Britain, Australia, and Canada. *JAMA* 302, 1437–1443. doi:10.1001/jama.2009.1409

Cromwell, I., van der Hoek, K., Melosky, B., and Peacock, S. (2011). Erlotinib or Docetaxel for Second-Line Treatment of Non-small Cell Lung Cancer: a Real-World Cost-Effectiveness Analysis. *J. Thorac. Oncol.* 6, 2097–2103. doi:10.1097/JTO.0b013e31822f657a

Cui, L., He, T., Jiang, Y., Li, M., Wang, O., Jiajue, R., et al. (2019). Predicting the Intervention Threshold for Initiating Osteoporosis Treatment Among Postmenopausal Women in China: a Cost-Effectiveness Analysis Based on Real-World Data. *Osteoporos. Int.* 31, 307–316. doi:10.1007/s00198-019-05173-6

Dakin, H., Devlin, N., Feng, Y., Rice, N., O'Neill, P., and Parkin, D. (2015). The Influence of Cost-Effectiveness and Other Factors on Nice Decisions. *Health Econ.* 24, 1256–1271. doi:10.1002/hec.3086

de Jong, L. A., Gout-Zwart, J. J., van den Bosch, M., Koops, M., and Postma, M. J. (2019). Rivaroxaban for Non-valvular Atrial Fibrillation and Venous Thromboembolism in the Netherlands: a Real-World Data Based Cost-Effectiveness Analysis. *J. Med. Econ.* 22, 306–318. doi:10.1080/13696998.2018.1563404

de Jong, L. A., Groeneveld, J., Stevanovic, J., Rila, H., Tieleman, R. G., Huisman, M. V., et al. (2019). Cost-effectiveness of Apixaban Compared to Other Anticoagulants in Patients with Atrial Fibrillation in the Real-World and Trial Settings. *PLoS One* 14, e0222658. doi:10.1371/journal.pone.0222658

de Pouvourville, G., Blin, P., and Karam, P. (2020). The Contribution of Real-World Evidence to Cost-Effectiveness Analysis: Case Study of Dabigatran Etexilate in France. *Eur. J. Health Econ.* 21, 235–249. doi:10.1007/s10198-019-01123-5

Deidda, M., Geue, C., Kreif, N., Dundas, R., and McIntosh, E. (2019). A Framework for Conducting Economic Evaluations Alongside Natural Experiments. *Soc. Sci. Med.* 220, 353–361. doi:10.1016/j.socscimed.2018.11.032

Di Marco, M., DAndrea, E., Panic, N., Baccolini, V., Migliara, G., Marzuillo, C., et al. (2018). Which Lynch Syndrome Screening Programs Could Be Implemented in the "real World"? A Systematic Review of Economic Evaluations. *Genet. Med.* 20 (10), 1131–1144. doi:10.1038/gim.2017.244

Djalalov, S., Beca, J., Hoch, J. S., Krahn, M., Tsao, M. S., Cutz, J. C., et al. (2014). Cost Effectiveness of EML4-ALK Fusion Testing and First-Line Crizotinib Treatment for Patients with Advanced ALK-Positive Non-small-cell Lung Cancer. *J. Clin. Oncol.* 32, 1012–1019. doi:10.1200/JCO.2013.53.1186

Dor, A., Luo, Q., Gerstein, M. T., Malveaux, F., Mitchell, H., and Markus, A. R. (2018). Cost-effectiveness of an Evidence-Based Childhood Asthma Intervention in Real-World Primary Care Settings. *J. Ambul. Care Manage.* 41, 213–224. doi:10.1097/JAC.0000000000000231

Drummond, M. F. (1996). The Future of Pharmacoeconomics: Bridging Science and Practice. *Clin. Ther.* 18, 969–968. doi:10.1016/s0149-2918(96)80053-1

Drummond, M. F., and McGuire, A. (2005). *Economic Evaluation in Health Care: Merging Theory with Practice*. Oxford, UK: Oxford University Press.

Eichler, H. G., Kong, S. X., Gerth, W. C., Mavros, P., and Jönsson, B. (2004). Use of Cost-Effectiveness Analysis in Health-Care Resource Allocation Decision-Making: How Are Cost-Effectiveness Thresholds Expected to Emerge? *Value Health* 7, 518–528. doi:10.1111/j.1524-4733.2004.75003.x

Fahr, P., Buchanan, J., and Wordsworth, S. (2019). A Review of the Challenges of Using Biomedical Big Data for Economic Evaluations of Precision Medicine. *Appl. Health Econ. Health Pol.* 17, 443–452. doi:10.1007/s40258-019-00474-7

Foglia, E., Bonfanti, P., Rizzardini, G., Bonizzoni, E., Restelli, U., Ricci, E., et al. (2013). Cost-utility Analysis of Lopinavir/ritonavir versus Atazanavir + Ritonavir Administered as First-Line Therapy for the Treatment of HIV Infection in Italy: from Randomised Trial to Real World. *PLoS One* 8, e57777. doi:10.1371/journal.pone.0057777

Gansen, F. M. (2018). Health Economic Evaluations Based on Routine Data in Germany: a Systematic Review. *BMC Health Serv. Res.* 18, 268. doi:10.1186/s12913-018-3080-3

Garrison, L. P., Jr, Neumann, P. J., Erickson, P., Marshall, D., and Mullins, C. D. (2007). Using Real-World Data for Coverage and Payment Decisions: the ISPOR Real-World Data Task Force Report. *Value Health* 10, 326–335. doi:10.1111/j.1524-4733.2007.00186.x

Gravelle, H., and Smith, D. (2001). Discounting for Health Effects in Cost-Benefit and Cost-Effectiveness Analysis. *Health Econ.* 10, 587–599. doi:10.1002/hec.618

Gruschkus, S. K., Lairson, D., Dunn, J. K., Risser, J., and Du, X. L. (2011). Cost-effectiveness of white Blood Cell Growth Factor Use Among a Large Nationwide Cohort of Elderly Non-hodgkin's Lymphoma Patients Treated with Chemotherapy. *Value Health* 14, 253–262. doi:10.1016/j.jval.2010.09.010

Hollier-Hann, G., Curry, A., Onishchenko, K., Akehurst, R., Ahmed, F., Davies, B., et al. (2020). Updated Cost-Effectiveness Analysis of onabotulinumtoxinA for the Prevention of Headache in Adults with Chronic Migraine Who Have Previously Received Three or More Preventive Treatments in the UK. *J. Med. Econ.* 23, 113–123. doi:10.1080/13696998.2019.1675417

Huang, M., Tian, Y., He, M., Liu, J., Ren, L., Gong, Y., et al. (2020). Crizotinib versus Chemotherapy: a Real-World Cost-Effectiveness Study in China. *J. Comp. Eff. Res.* 9, 93–102. doi:10.2217/cer-2019-0075

Hudson, K. L., and Collins, F. S. (2017). The 21st Century Cures Act - A View from the NIH. *N. Engl. J. Med.* 376, 111–113. doi:10.1056/NEJMp1615745

Hughes-Wilson, W., Palma, A., Schuurman, A., and Simoens, S. (2012). Paying for the Orphan Drug System: Break or bend? Is it Time for a New Evaluation System for Payers in Europe to Take Account of New Rare Disease Treatments?. *Orphanet J. Rare Dis.* 7, 74. doi:10.1186/1750-1172-7-74

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., et al. (2013). Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and Elaboration: a Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 16 (2), 231–250. doi:10.1016/j.jval.2013.02.002

Isla-Tejera, B., Ruano, J., Alvarez, M. A., Brieva, T., Cárdenas, M., Baamonde, C., et al. (2013). Economic Evaluation of Botulinum Toxin versus Thoracic Sympathectomy for Palmar Hyperhidrosis: Data from a Real-World Scenario. *Dermatol. Ther. (Heidelb)* 3 (1), 63–72. doi:10.1007/s13555-013-0025-y

Jönsson, B. (2015). Bringing in Health Technology Assessment and Cost-Effectiveness Considerations at an Early Stage of Drug Development. *Mol. Oncol.* 9 (5), 1025–1033. doi:10.1016/j.molonc.2014.10.009

Kaiser, C., Brunner-La Rocca, H. P., Buser, P. T., Bonetti, P. O., Osswald, S., Linka, A., et al. (2005). Incremental Cost-Effectiveness of Drug-Eluting Stents Compared with a Third-Generation Bare-Metal Stent in a Real-World Setting: Randomised Basel Stent Kosten Effektivitäts Trial (BASKET). *Lancet* 366, 921–929. doi:10.1016/S0140-6736(05)67221-2

Kemp, L., Haughney, J., Barnes, N., Sims, E., von Ziegenweidt, J., Hillyer, E. V., et al. (2010). Cost-effectiveness Analysis of Corticosteroid Inhaler Devices in Primary Care Asthma Management: A Real World Observational Study. *Clinicoecon Outcomes Res.* 2, 75–85. doi:10.2147/ceor.s10835

Khor, S., Beca, J., Krahn, M., Hodgson, D., Lee, L., Crump, M., et al. (2014). Real World Costs and Cost-Effectiveness of Rituximab for Diffuse Large B-Cell Lymphoma Patients: a Population-Based Analysis. *BMC Cancer* 14, 586. doi:10.1186/1471-2407-14-586

Koto, P. S., Hu, S. X., Virani, K., Simpkin, W. L., Christian, C. A., Cao, H., et al. (2019). A Cost-Utility Analysis of Endovascular Thrombectomy in a Real-World Setting. *Can. J. Neurol. Sci.* 47, 1–11. doi:10.1017/cjn.2019.308

Lairson, D. R., Parikh, R. C., Cormier, J. N., and Du, X. L. (2014). Cost-utility Analysis of Platinum-Based Chemotherapy versus Taxane and Other Regimens for Ovarian Cancer. *Value Health* 17, 34–42. doi:10.1016/j.jval.2013.11.007

Landstedt-Hallin, L., Gundgaard, J., Ericsson, Å., and Ellfors-Zetterlund, S. (2017). Cost-effectiveness of Switching to Insulin Degludec from Other Basal Insulins: Evidence from Swedish Real-World Data. *Curr. Med. Res. Opin.* 33, 647–655. doi:10.1080/03007995.2016.1277194

Lang, H. C., Chen, H. W., Chiou, T. J., and Chan, A. L. (2016). The Real-World Cost-Effectiveness of Adjuvant Trastuzumab in HER-2/neu-Positive Early Breast Cancer in Taiwan. *J. Med. Econ.* 19, 923–927. doi:10.1080/13696998.2016.1185013

Langer, J., Wolden, M. L., Shimoda, S., Sato, M., and Araki, E. (2019). Short-Term Cost-Effectiveness of Switching to Insulin Degludec in Japanese Patients with Type 2 Diabetes Receiving Basal-Bolus Therapy. *Diabetes Ther.* 10, 1347–1356. doi:10.1007/s13300-019-0635-1

Lekander, I., Borgström, F., Svarvar, P., Ljung, T., Carli, C., and van Vollenhoven, R. F. (2010). Cost-effectiveness of Real-World Infliximab Use in Patients with Rheumatoid Arthritis in Sweden. *Int. J. Technol. Assess. Health Care* 26, 54–61. doi:10.1017/S0266462309990596

Lekander, I., Kobelt, G., Svarvar, P., Ljung, T., van Vollenhoven, R., and Borgström, F. (2013). The Comparison of Trial Data-Based and Registry Data-Based Cost-Effectiveness of Infliximab Treatment for Rheumatoid Arthritis in Sweden Using a Modeling Approach. *Value Health* 16, 251–258. doi:10.1016/j.jval.2012.11.002

Li, N., Yang, X., Fan, L., Totev, T., Guerin, A., Chen, L., et al. (2017). Nilotinib versus Dasatinib as Second-Line Therapy in Patients with Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase Who Are Resistant or Intolerant to Imatinib: a Cost-Effectiveness Analysis Based on Real-World Data. *J. Med. Econ.* 20, 328–336. doi:10.1080/13696998.2016.1261032

Liao, C. H., Tan, E. C., Chen, C. C., and Yang, M. C. (2017). Real-world Cost-Effectiveness of Laparoscopy versus Open Colectomy for colon Cancer: a Nationwide Population-Based Study. *Surg. Endosc.* 31, 1796–1805. doi:10.1007/s00464-016-5176-3

Liljas, B. (1998). How to Calculate Indirect Costs in Economic Evaluations. *Pharmacoeconomics* 13 (Pt 1), 1–7. doi:10.2165/00019053-199813010-00001

Lin, C. Y., Fang, H. Y., Feng, C. L., Li, C. C., and Chien, C. R. (2016). Cost-effectiveness of Neoadjuvant Concurrent Chemoradiotherapy versus Esophagectomy for Locally Advanced Esophageal Squamous Cell Carcinoma: A Population-Based Matched Case-Control Study. *Thorac. Cancer* 7, 288–295. doi:10.1111/1759-7714.12326

Lin, L. W., Teng, G. G., Lim, A. Y. N., Yoong, J. S., Zethraeus, N., and Wee, H. L. (2019). Cost-effectiveness of an Adherence-Enhancing Intervention for Gout Based on Real-World Data. *Int. J. Rheum. Dis.* 22, 545–554. doi:10.1111/1756-185X.13446

Lindgren, P., Geborek, P., and Kobelt, G. (2009). Modeling the Cost-Effectiveness of Treatment of Rheumatoid Arthritis with Rituximab Using Registry Data from Southern Sweden. *Int. J. Technol. Assess. Health Care* 25, 181–189. doi:10.1017/S0266462309090230

Mabin, T. A., and Condolfi, P. (2014). An Analysis of Real-World Cost-Effectiveness of TAVI in South Africa. *Cardiovasc. J. Afr.* 25, 21–26. doi:10.5830/CVJA-2013-090

Makady, A., van Veelen, A., Jonsson, P., Moseley, O., D'Andon, A., de Boer, A., et al. (2018). Using Real-World Data in Health Technology Assessment (HTA) Practice: A Comparative Study of Five HTA Agencies. *Pharmacoeconomics* 36, 359–368. doi:10.1007/s40273-017-0596-z

McNamee, R. (2005). Regression Modelling and Other Methods to Control Confounding. *Occup. Environ. Med.* 62, 5006. doi:10.1136/oem.2002.001115

McQueen, R. B., Sheehan, D. N., Whittington, M. D., van Boven, J. F. M., and Campbell, J. D. (2018). Cost-Effectiveness of Biological Asthma Treatments: A Systematic Review and Recommendations for Future Economic Evaluations. *Pharmacoeconomics* 36 (8), 957–971. doi:10.1007/s40273-018-0658-x

Mehta, N., and Pandit, A. (2018). Concurrence of Big Data Analytics and Healthcare: A Systematic Review. *Int. J. Med. Inform.* 114, 57–65. doi:10.1016/j.ijmedinf.2018.03.013

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G.PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *Plos Med.* 6, e1000097. doi:10.1371/journal.pmed.1000097

Nilsson, F. O., Linnér, L., Samuelsson, E., and Milsom, I. (2012). Cost-effectiveness Analysis of Newer Anticholinergic Drugs for Urinary Incontinence vs Oxybutynin and No Treatment Using Data on Persistence from the Swedish Prescribed Drug Registry. *BJU Int.* 110, 240–246. doi:10.1111/j.1464-410X.2011.10729.x

Ofman, J. J., Sullivan, S. D., Neumann, P. J., Chiou, C. F., Henning, J. M., Wade, S. W., et al. (2003). Examining the Value and Quality of Health Economic Analyses: Implications of Utilizing the QHES. *J. Manag. Care Pharm.* 9, 53–61. doi:10.18553/jmcp.2003.9.1.53

Ohsfeldt, R. L., Gandhi, S. K., Fox, K. M., and McKenney, J. M. (2018). Statin Cost-Effectiveness Comparisons Using Real-World Effectiveness Data: Formulary Implications. *Value Health* 11, 1061–1069. doi:10.1111/j.1524-4733.2008.00354.x

Olivares, J. M., Rodriguez-Martinez, A., Burón, J. A., Alonso-Escolano, D., and Rodriguez-Morales, A.e-STAR Study Group (2008). Cost-effectiveness Analysis of Switching Antipsychotic Medication to Long-Acting Injectable Risperidone in Patients with Schizophrenia : a 12- and 24-month Follow-Up from the E-STAR Database in Spain. *Appl. Health Econ. Health Pol.* 6, 41–53. doi:10.2165/00148365-200806010-00004

Ou, H. T., Chen, Y. T., Liu, Y. M., and Wu, J. S. (2016). Comparative Cost-Effectiveness of Metformin-Based Dual Therapies Associated with Risk of Cardiovascular Diseases Among Chinese Patients with Type 2 Diabetes: Evidence from a Population-Based National Cohort in Taiwan. *Diabetes Res. Clin. Pract.* 116, 14–25. doi:10.1016/j.diabres.2016.03.013

Parody-Rúa, E., Rubio-Valera, M., Guevara-Cuellar, C., Gómez-Lumbreras, A., Casajuana-Closas, M., Carbonell-Duacastella, C., et al. (2020). Economic Evaluations Informed Exclusively by Real World Data: A Systematic Review. *Int. J. Environ. Res. Public Health* 17, 1171. doi:10.3390/ijerph17041171

Peng, S., Deger, K. A., Ustyugova, A., Gandhi, P., Qiao, N., Wang, C., et al. (2018). Cost-effectiveness Analysis of Dabigatran versus Rivaroxaban for Stroke Prevention in Patients with Non-valvular Atrial Fibrillation Using Real-World Evidence in Elderly US Medicare Beneficiaries. *Curr. Med. Res. Opin.* 34, 55–63. doi:10.1080/03007995.2017.1375470

Price, D., Asukai, Y., Ananthapavan, J., Malcolm, B., Radwan, A., and Keyzor, I. (2013). A UK-based Cost-Utility Analysis of Indacaterol, a Once-Daily Maintenance Bronchodilator for Patients with COPD, Using Real World Evidence on Resource Use. *Appl. Health Econ. Health Pol.* 11, 259–274. doi:10.1007/s40258-013-0021-5

Redig, J., Dalén, J., Harmenberg, U., Lindskog, M., Ljungberg, B., Lundstam, S., et al. (2019). Real-world Cost-Effectiveness of Targeted Therapy in Metastatic Renal Cell Carcinoma in Sweden: a Population-Based Retrospective Analysis. *Cancer Manag. Res.* 11, 1289–1297. doi:10.2147/CMAR.S188849

Rognoni, C., Ciani, O., Sommariva, S., and Tarricone, R. (2017). Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. *Value Health* 20, 336–344. doi:10.1016/j.jval.2016.09.2397

Ronaldson, S. J., Raghunath, A., Torgerson, D. J., and Van Staa, T. (2017). Cost-effectiveness of Antibiotics for COPD Management: Observational Analysis Using CPRD Data. *ERJ Open Res.* 3, 00085–02016. doi:10.1183/23120541.00085-2016

Rubio-Valera, M., Peñarrubia-María, M. T., Iglesias-González, M., Knapp, M., McCrone, P., Roig, M., et al. (2019). Cost-effectiveness of Antidepressants versus Active Monitoring for Mild-To-Moderate Major Depressive Disorder: a Multisite Non-randomized-controlled Trial in Primary Care (INFAP Study). *Eur. J. Health Econ.* 20, 703–713. doi:10.1007/s10198-019-01034-5

Schulman, S., Shortt, B., Robinson, M., and Eikelboom, J. W. (2013). Adherence to Anticoagulant Treatment with Dabigatran in a Real-World Setting. *J. Thromb. Haemost.* 11, 1295–1299. doi:10.1111/jth.12241

Silverman, S. L. (2009). From Randomized Controlled Trials to Observational Studies. *Am. J. Med.* 122, 114–120. doi:10.1016/j.amjmed.2008.09.030

Sullivan, P. W., Li, Q., Bilir, S. P., Dang, J., Kavati, A., Yang, M., et al. (2020). Cost-effectiveness of Omalizumab for the Treatment of Moderate-To-Severe Uncontrolled Allergic Asthma in the United States. *Curr. Med. Res. Opin.* 36, 23–32. doi:10.1080/03007995.2019.1660539

Tanaka, E., Inoue, E., Yamaguchi, R., Shimizu, Y., Kobayashi, A., Sugimoto, N., et al. (2017). Pharmacoeconomic Analysis of Biological Disease Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis Based on Real-World Data from the IORRA Observational Cohort Study in Japan. *Mod. Rheumatol.* 27, 227–236. doi:10.1080/14397595.2016.1205799

Tarride, J. E., Hopkins, R., Blackhouse, G., Bowen, J. M., Bischof, M., Von Keyserlingk, C., et al. (2010). A Review of Methods Used in Long-Term Cost-Effectiveness Models of Diabetes Mellitus Treatment. *Pharmacoeconomics* 28, 255–277. doi:10.2165/11531590-000000000-00000

Terkola, R., Antoñanzas, F., and Postma, M. (2017). Economic Evaluation of Personalized Medicine: a Call for Real-World Data. *Eur. J. Health Econ.* 18, 1065–1067. doi:10.1007/s10198-017-0890-x

Thein, H. H., Qiao, Y., Zaheen, A., Jembere, N., Sapisochin, G., Chan, K. K. W., et al. (2017). Cost-effectiveness Analysis of Treatment with Non-curative or Palliative Intent for Hepatocellular Carcinoma in the Real-World Setting. *PLoS One* 12, e0185198. doi:10.1371/journal.pone.0185198

Thijssen, J., van den Akker van Marle, M. E., Borleffs, C. J., van Rees, J. B., de Bie, M. K., van der Velde, E. T., et al. (2014). Cost-effectiveness of Primary Prevention Implantable Cardioverter Defibrillator Treatment: Data from a Large Clinical Registry. *Pacing Clin. Electrophysiol.* 37, 25–34. doi:10.1111/pace.12238

Thronicke, A., Reinhold, T., von Trott, P., Matthes, H., and Schad, F. (2020). Cost-Effectiveness of Real-World Administration of Concomitant *Viscum Album* L. Therapy for the Treatment of Stage IV Pancreatic Cancer. *Evid. Based Complement. Alternat Med.* 2020, 3543568. doi:10.1155/2020/3543568

Tsai, P. C., Liu, T. W., Huang, C. F., Yeh, M. L., Dai, C. Y., Chuang, W. L., et al. (2018). A Real World Cost Effectiveness Analysis of Interferon-Based Therapy for HCV naïve Super-responders. *J. Chin. Med. Assoc.* 81, 670–675. doi:10.1016/j.jcma.2017.05.015

van Gils, C. W., de Groot, S., Redekop, W. K., Koopman, M., Punt, C. J., and Uyl-de Groot, C. A. (2013). Real-world Cost-Effectiveness of Oxaliplatin in Stage III colon Cancer: a Synthesis of Clinical Trial and Daily Practice Evidence. *Pharmacoeconomics* 31, 703–718. doi:10.1007/s40273-013-0061-6

van Leent, M. W., Stevanović, J., Jansman, F. G., Beinema, M. J., Brouwers, J. R., and Postma, M. J. (2015). Cost-Effectiveness of Dabigatran Compared to Vitamin-K Antagonists for the Treatment of Deep Venous Thrombosis in the Netherlands Using Real-World Data. *PLoS One* 10, e0135054. doi:10.1371/journal.pone.0135054

Vassall, A., Siapka, M., Foster, N., Cunnama, L., Ramma, L., Fielding, K., et al. (2017). Cost-effectiveness of Xpert MTB/RIF for Tuberculosis Diagnosis in South Africa: a Real-World Cost Analysis and Economic Evaluation. *Lancet Glob. Health* 5, e710–e719. doi:10.1016/S2214-109X(17)30205-X

Voermans, A. M., Mewes, J. C., Broyles, M. R., and Steuten, L. M. G. (2019). Cost-Effectiveness Analysis of a Procalcitonin-Guided Decision Algorithm for Antibiotic Stewardship Using Real-World U.S. Hospital Data. *OMICS* 23, 508–515. doi:10.1089/omi.2019.0113

Wang, H., Wang, M., Wang, J., Liu, H., Lu, R., Duan, T., et al. (2019). Cost-effectiveness Analysis of Comprehensive Intervention Programs to Control Blood Glucose in Overweight and Obese Type 2 Diabetes Mellitus Patients Based on a Real-World Setting: Markov Modeling. *Ann. Transl Med.* 7, 676. doi:10.21037/atm.2019.10.38

Wei, W., Buysman, E., Grabner, M., Xie, L., Brekke, L., Ke, X., et al. (2017). A Real-World Study of Treatment Patterns and Outcomes in US Managed-Care Patients with Type 2 Diabetes Initiating Injectable Therapies. *Diabetes Obes. Metab.* 19, 375–386. doi:10.1111/dom.12828

Wordsworth, S., Doble, B., Payne, K., Buchanan, J., Marshall, D. A., McCabe, C., et al. (2018). Using "Big Data" in the Cost-Effectiveness Analysis of Next-Generation Sequencing Technologies: Challenges and Potential Solutions. *Value Health* 21, 1048–1053. doi:10.1016/j.jval.2018.06.016

Yang, B. M., Bae, E. Y., and Kim, J. (2008). Economic Evaluation and Pharmaceutical Reimbursement Reform in South Korea's National Health Insurance. *Health Aff. (Millwood)* 27, 179–187. doi:10.1377/hlthaff.27.1.179

Yang, J. J., Park, S. K., Cho, L. Y., Han, W., Park, B., Kim, H., et al. (2010). Cost-effectiveness Analysis of 5 Years of Postoperative Adjuvant Tamoxifen Therapy for Korean Women with Breast Cancer: Retrospective Cohort Study of the Korean Breast Cancer Society Database. *Clin. Ther.* 32, 1122–1138. doi:10.1016/j.clinthera.2010.05.013

Yong, J. H., Masucci, L., Hoch, J. S., Sujic, R., and Beaton, D. (2016). Cost-effectiveness of a Fracture Liaison Service-Aa Real-World Evaluation after 6 Years of Service Provision. *Osteoporos. Int.* 27, 231–240. doi:10.1007/s00198-015-3280-1

Zhao, Y. J., Lin, L., Zhou, H. J., Tan, K. T., Chew, A. P., Foo, C. G., et al. (2016). Cost-effectiveness Modelling of Novel Oral Anticoagulants Incorporating Real-World Elderly Patients with Atrial Fibrillation. *Int. J. Cardiol.* 220, 794–801. doi:10.1016/j.ijcard.2016.06.087

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Cost-Effectiveness Analysis of Direct Oral Anticoagulants Versus Vitamin K Antagonists for Venous Thromboembolism in China

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Background: The drug therapy of venous thromboembolism (VTE) presents a significant economic burden to the health-care system in low- and middle-income countries. To understand which anticoagulation therapy is most cost-effective for clinical decision-making , the cost-effectiveness of apixaban (API) versus rivaroxaban (RIV), dabigatran (DAB), and low molecular weight heparin (LMWH), followed by vitamin K antagonist (VKA), in the treatment of VTE in China was assessed.

Methods: To access the quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs), a long-term cost-effectiveness analysis was constructed using a Markov model with 5 health states. The Markov model was developed using patient data collected from the Xijing Hospital from January 1, 2016 to January 1, 2021. The time horizon was set at 30 years, and a 6-month cycle length was used in the model. Costs and ICERs were reported in 2020 U.S. dollars. One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were used to test the uncertainties. A Chinese health-care system perspective was used.

Results: In the base case, the data of 231 VTE patients were calculated in the base case analysis retrospectively. The RIV group resulted in a mean VTE attributable to 95% effective treatment. API, DAB, and VKA have a negative ICER (–187017.543, –284,674.922, and –9,283.339, respectively) and were absolutely dominated. The Markov model results confirmed this observation. The ICER of the API and RIV was negative (–216176.977), which belongs to the absolute inferiority scheme, and the ICER value of the DAB and VKA versus RIV was positive (110,577.872 and 836,846.343). Since the ICER of DAB and VKA exceeds the threshold, RIV therapy was likely to be the best choice for the treatment of VTE within the acceptable threshold range. The results of the sensitivity analysis revealed that the model output varied mostly with the cost in the DAB on-treatment therapy. In a probabilistic sensitivity analysis of 1,000 patients for 30 years, RIV has 100% probability of being cost-effective compared with other regimens when the WTP is $10973 per QALY. When WTP exceeded $148,000, DAB was more cost-effective than RIV.

Conclusions: Compared with LMWH + VKA and API, the results proved that RIV may be the most cost-effective treatment for VTE patients in China. Our findings could be helpful for physicians in clinical decision-making to select the appropriate treatment option for VTE.

Keywords: VTE, DOAC, CEA = cost-effectiveness analysis, China, LMWH (low molecular weight heparin)

HIGHLIGHTS

"What is already known about this subject":

- VTE is a significant cause of morbidity and mortality worldwide and is associated with a substantial economic burden.
- The most cost-effective anticoagulant treatment option for VTE remains controversial.

"What this study adds":

- RIV is likely to be considered a cost-effective or cost-saving strategy for VTE patients in China.
- When the willingness to pay exceeded $148,000, DAB was more cost-effective than RIV.
- This study could support the decision-making of stakeholders in China, including hospitals, payers, and physicians.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common clinical peripheral vascular disease and disproportionately impacts adults worldwide (Gould et al., 2012; Nemeth et al., 2019; Chopard et al., 2020). An estimated one in 12 people older than 45 years will be at risk of VTE (Cushman et al., 2020). The mortality of VTE can be as high as 10–30% within one month in high-risk patients (Renner and Barnes, 2020). The economic burden caused by VTE can reach one billion or even tens of billions of dollars each year in European countries (Di Nisio et al., 2016; Barco et al., 2020). Compared with Western countries, Asian populations are known to have lower VTE incidences, which are estimated to be approximately 15–20% of the level recorded in Western countries (Raskob et al., 2014). However, the detection rate of VTE in the Asian population has increased greatly in recent years with the improvement of diagnostic levels and diagnostic awareness (Lee et al., 2017). Especially, the hospitalization rate in China is, indeed, increasing from 3.2 to 17.5 per 100,000 population (Angchaisuksiri et al., 2021) due to the increase in the age of the population, the incidence of cancer, and the number of operations (Zhai et al., 2019). Moreover, considering the risk of death from the disease, patients often stay in the hospital for longer periods, which will impose a greater social and economic burden on the health-care system (Zhang et al., 2019).

Current guidelines (Kakkos et al., 2020) for the management of VTE in 2021 recommended the use of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) for the initial and secondary treatment of VTE. Low molecular weight heparin (LMWH) overlapped with VKAs has been considered a standard treatment for many years. Recently, DOACs have been increasing in popularity and availability, including apixaban (API), rivaroxaban (RIV), and dabigatran (DAB) (Ortel et al., 2020). A 2014 review (Wu et al., 2014a, b) comparing the results of five randomized clinical trials has identified that DOACs have similar efficacy to VKA in the treatment of VTE but significantly reduce the risk of major bleeding (MB). Moreover, DOACs do not require monitoring, take effect quickly, and avoid bridging with load and LMWH (López-López et al., 2017). However, the drug acquisition cost of DOACs was higher than that of VKA (US$39.47/2.5 mg versus 0.18/2.5 mg) according to data from the IQVIA China Hospital Pharmaceutical Audit Database. Although Chinese medical insurance can only partially reimburse the cost of DOACs (70–80%), it is limited to patients with non-valvular atrial fibrillation and lower extremity joint replacement surgery.

Up to now, the National Institute for Health and Care Excellence (NICE) guideline (Howard and Hughes, 2013) team pointed out that the most cost-effective therapy should be treated with caution and is still controversial. Lanitis (Lanitis et al., 2016) conducted a pharmacoeconomic analysis based on the AMPILIFY (Li:QY et al., 2015) clinical trial in 2016. The results showed that API is a cost-effective therapeutic option versus the standard therapy for VTE. Nevertheless, the NICE constructed a cost–utility analysis from an NHS/personal social perspective, which showed that the costs were partially offset by fewer surveillance visits and lower resource usage associated with managing major bleeding events (Schulman et al., 2020). The economic research conducted in China has also differed results. One cost-effectiveness (Xiaoyu et al., 2016) strategy based on two RCTs indicated that the use of API for VTE does not represent a good value for the cost at the acceptable threshold in China. A 2020 literature (Wang Sheng-xiang et al., 2020) whose probability was determined by meta-analysis showed that RIV had economic advantages over standard therapies and other DOACs. It can be seen that most studies are based on literature research or RCT evidence. However, RCT evidence has strict inclusion and exclusion criteria, which makes it difficult to extrapolate the research results to clinical practice (Sanson-Fisher et al., 2007). In addition, the existing economic evaluations mainly focused on the comparison of one DOAC versus VKA or different DOACs. Nonetheless, only comparing the results of two interventions once may not help clinicians to choose the best option when several treatment options coexist.

The objective of this study is to compare the cost-effectiveness of four regimens at the same time both in the short-term

hospitalization period and long-term Markov model in VTE from the Chinese health-care system's perspective. In this way, the results of this study will provide for clinical decision-making in VTE patients and the optimization of health-care resource allocation.

METHODS

The patient data were retrospectively obtained from the EMR database of VTE patients at Xijing Hospital in Xi'an, China, from January 1, 2016 to January 1, 2021. The study was approved by the Xijing Hospital Institutional Review Board (KY20212011-C-1). The guideline checklist reported in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) was followed (Kong et al., 2009; Weinstein et al., 2010; Husereau et al., 2013).

Patients and Intervention

Inclusion criteria: 1) Patients diagnosed with VTE according to the European Society for Vascular Surgery (ESVS) 2021 Guidelines; 2) Anticoagulant drugs used by patients are one of the following: API, RIV, DAB, and LMAH + VKA; 3) age>18 years old; and 4) the data and medical records are complete.

Exclusion criteria: 1) Patients have anticoagulation contraindications; 2) patients who have not completed standardized treatment in this hospital and are discharged automatically; and 3) drug abuse or mental illness that may interfere with treatment.

Usage and Dosage of Drugs

The dose and course of treatment are determined according to the guidelines recommended (Kakkos et al., 2020; Renner and Barnes, 2020): anticoagulation therapy strategies should be conceptualized in 3 phases: initial management (5–21 days), primary treatment (3–6 months), and secondary prevention (beyond 3–6 months). Based on the recommendation, rivaroxaban was prescribed at a dose of 15mg, BID for 21 days, followed by 20 mg once daily until 6 months. Apixaban treatment consisted of a 7-day course of 10 mg twice a day, followed by 5 mg twice a day. Patients with dabigatran therapy take LMWH 0.6 ml/6000 IU, BID from day 1 to 5, then stop and use dabigatran 150 mg twice daily. For patients who will be transitioning to warfarin, LMWH is commonly used in the primary treatment phase, followed by 5 mg warfarin daily adjusted to the target INR 2.0–3.0.

Adverse reactions such as MB, clinically relevant non-major bleeding (CRNMB), and death in the patient were observed and recorded within the hospitalization period. Major bleeding was defined as clinically significant and associated with a reduction in hemoglobin levels of at least 20 g/L, or bleeding occurring in a critical site (Schulman et al., 2005). CRNMB was defined as any significant bleeding not fitting the criteria for major bleeding (Kaatz et al., 2015). Means and standard deviations (SD) of all types of resource utilizations were calculated.

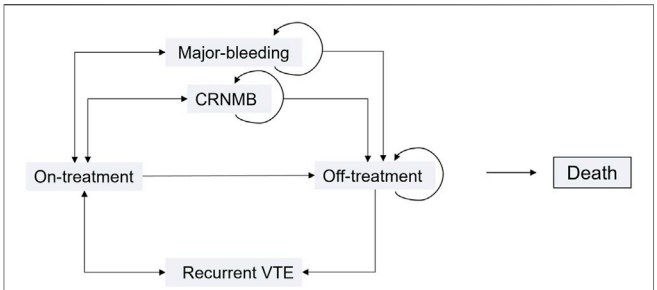

FIGURE 1 | Markov state transition model.

Model Structure

A long-run Markov model was developed to evaluate the cost-effectiveness analysis, which estimated the costs and health outcomes of treating VTE using DOACs in patients. The Markov state transition model is shown in **Figure 1**. The process included six discrete health states: VTE on-treatment, VTE off-treatment, recurrent VTE, MB, CRNMB, and the absorbing state of death. Patients entered the model with "on-treatment" status after diagnosis of VTE. The initial assessment and treatment differences by physicians and providers were ignored, assuming that these costs were the same between groups. Only costs after treatment were assessed. A cohort of individuals aged 59 years was followed in the model which was calculated from the base case. Off-treatment refers to stopping treatment for any reason after the individual expects the treatment to end. Patients can progress from any other health state than the CRNMB state to the death health state. The same patient can only experience one of the predicted states or remain unchanged in the current health state. Because the American Society of Hematology 2020 guidelines recommended (Ortel et al., 2020) that primary treatment continues anticoagulant therapy for 3–6 months for the treatment of VTE, we set the cycle length to be 6 months. The time horizon was set to be 30 years. To calculate the dosage of LMWH and warfarin, we assumed a typical patient weighed 60 kg.

Model Input

All model parameters collected in this study mainly consisted of cost, transition probability, and health utility value (**Table 1**). The clinical effects and cost parameters were quoted from electronic medical records (EMR) at Xijing Hospital. Based on previous studies, the transition probabilities between different health states were estimated. Some other outcome probabilities and utilization data were obtained from the literature review. The following formula (Briggs and Sculpher, 1998; Petitti, 2002) was used to calculate the transition probabilities of one cycle: $r = -[\ln(1-P_1)]/t_1$; $P_2 = 1-\exp(-rt_2)$; r represents the transient probability, and P_1 and P_2 represent the transition probability for a given cycle t_1 and t_2, respectively. Moreover, this study assumed the blank data by asking for expert advice.

For comparability, all costs were expressed in U.S. dollars for the 2021 reference year in this study. Chinese yuan (CNY) was converted into U.S. dollars by using the following exchange rate:

TABLE 1 | Model inputs.

Cost in different states	Base case	Range tested	Distribution	Source
Recurrent VTE	3,853	2,697–5,009	Gamma	LI
MB	3,834	2,684–4,984	Gamma	Wu(Wu et al.)
CRNMB	8.25	5.77–10.72	Gamma	Wu(Wu et al.)
Warfarin monitoring (per time)	10.98	7.69–14.27	Gamma	EMR
Utilities				
VTE on-treatment	0.94	0.75–1.00	Beta	Mccullagh (Mccullagh et al., 2012)
Recurrent VTE	0.76	0.57–0.95	Beta	Uniform
MB	0.55	0.15–0.86	Beta	Hogg (Hogg et al., 2013)
CRNMB	0.61	0.68–0.51	Beta	Locadia (Locadia et al., 2004)
Death	0.00	-	Beta	Definition
VTE off-treatment	0.75	0.45–0.91	Beta	-
API	−0.0020	0.000–0.0060	Beta	Gage(Gage et al., 1996)
VKA	−0.0130	0.000–0.0047	Beta	Gage(Gage et al., 1996)
RIV	−0.002	0.000–0.006	Beta	Gage(Gage et al., 1996)
DAB	−0.002	0.000–0.005	Beta	Gage(Gage et al., 1996)
Cost of drugs				
API	5,877.399	639.764–14,326.537	Gamma	EMR
RIV	3,072.136	465.279–18,391.693	Gamma	EMR
DAB	3,926.160	970.546–13,152.974	Gamma	EMR
VKA	4,325.386	612.487–10,287.356	Gamma	EMR

VTE, venous thromboembolism; MB, major bleeding; CRNMB, clinically relevant non-major bleeding; API, apixaban; VKA, vitamin K antagonist; RIV, rivaroxaban; DAB, dabigatran; EMR, electronic medical records.

1US$ = CNY6.46 (2020). From the Chinese health-care perspective and considering the proportion of direct medical costs and direct non-medical costs to direct costs, the cost of this study is proposed as direct medical costs. Utility level values for other health states were obtained from the literature search. According to the current pharmacoeconomic guidelines in China (Liu et al., 2015; Paulden et al., 2017), the discount rate used in this study is 5% (0–8%).

Outcomes

The primary result is the incremental cost-effectiveness ratio (ICER) to evaluate and select multiple programs, presented in costs per quality-adjusted life year (QALY). In this study, the lowest cost-effectiveness ratio (CER) treatment therapy in each group was used as the control. The ICER between other plans and the control treatment therapy was calculated separately to analyze the choice of the most cost-effective therapy. According to the World Health Organization (WHO, 2003) guidelines, if the additional cost of switching to a new treatment plan to obtain an additional effect is less than three times the country-specific per capita gross domestic product (GDP), then the treatment plan is considered acceptable by the patient. It was regarded as cost-effective if the ICER was less than per capita GDP. Therefore, this study sets the value that people will pay as one to three times of GDP (10,973–32,921$/year) in 2020 (Guo, 2020). To determine the most cost-effective option using net life years or QALY gained, 1,000 iterations of Monte Carlo simulations were performed to construct the acceptability curve of the therapies.

Statistical Analysis

Measurement data were expressed as mean ± standard deviation. Model development, implementation, and analysis were performed using TreeAge Pro (TreeAge Software, Inc., Williamstown, MA, United States) for queue simulation and sensitivity analysis. The Markov model cycle length was set as 6 months.

The Markov model parameters in this study are derived from the EMR database. Due to the differences in research design, data statistics, and research conditions, sensitivity analysis was carried out to correct the model (Naimark et al., 2008). One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to access the uncertainty in the model. The study used 95% CIs as the upper and lower limits of the health state utilities. A range of ±20% of the base-case value was used for costs.

The results of one-way sensitivity analysis were displayed in the form of tornado diagrams. The variables that have the greatest impact on the collaboration results were drawn in turn. By defining the distribution for key parameters (utilities were defined as beta distribution and gamma distribution for costs), probablistic sensitivity analysis (PSA) was performed to assess the overall impact of the model's uncertainty. Monte Carlo simulation was performed 1,000 times to analyze multiple uncertain factors, which are represented by the cost-effectiveness acceptable curve and ICER scatter diagram. The results of the PSA were described as scatterplots.

RESULTS

Base-Case Analysis

A total of 551 patients with VTE were collected. Two hundred one patients were excluded because of the incomplete data. Ninety-eight patients who were not on a single drug medication and 21

TABLE 2 | Comparison of the baseline characteristics of the four groups.

Characteristic	Apixaban (N = 50)	Rivaroxaban (N = 110)	Dabigatran (N = 21)	LMWH/VKA (N = 50)
Age (yr)				
Mean	58 ± 16.3	62 ± 11.5	64 ± 14.6	53 ± 13.6
Range	24–94	29–87	32–92	19–75
Age category (years), n (%)				
<75	78	86.4	81.0	94.0
≥75	22	13.6	19.0	6.0
Female sex, no. (%)	50.0	42.7	52.4	50.0
Weight (kg)				
Mean	65 ± 11.8	77 ± 11.1	65 ± 10.2	66 ± 1.0
Range	40–90	46–95	50–80	45–96
BMI (kg/m^2)	23 ± 3.3	23 ± 6.4	25 ± 3.2	24 ± 3.0
Length of hospital stay				
Mean	8 ± 6.2	9 ± 7.6	11 ± 10.1	10 ± 8.4
Range	1–29	1–51	2–48	3–56
Diabetes mellitus, no. (%)	2.0	8.2	19.0	2.0
Hypertension, no. (%)	18.0	33.6	19.0	10.0
Type of index event, no. (%)				
DVT only	98.0	30.0	80.9	32.0
PE only	0.0	29.1	19.1	38.0
Both DVT and PE	2.0	40.9	0.0	30.0

BMI: body mass index, API, apixaban; RIV, rivaroxaban; DAB, dabigatran; LMWH/VKA, low molecular weight heparin followed by vitamin K antagonist. DVT, deep vein thrombosis; PE, pulmonary embolism.

TABLE 3 | Results of EMR data for hospitalization costs.

	Laboratory costs	Bed costs	Operation costs	Nursing costs	Radiation costs	Examination costs	Treatment costs	Medicine costs	Diagnosis costs	Transfusion costs	Total
API	227.19	42.69	745.16	28.29	143.08	226.58	5,581.44	947.98	27.52	346.28	5,877.39
RIV	472.41	48.48	1,053.4	65.31	114.88	350.38	1,515.54	1,105.24	35.68	477.44	3,072.13
DAB	338.21	75.05	1,165.71	41.40	101.26	309.75	1,428.48	715.78	47.91	486.07	3,926.16
LMWH/ VKA	572.98	58.87	866.24	89.03	151.27	516.34	1,523.18	2056.08	28.91	278.44	4,325.38

API, apixaban; RIV, rivaroxaban; DAB, dabigatran; LMWH/VKA, low molecular weight heparin followed by vitamin K antagonist.

TABLE 4 | Therapy efficacy and safety results.

	API (N = 50)	RIV (N = 110)	DAB (N = 21)	LMWH/VKA (N = 50)
Efficacy (%)				
Cure	22.0	2.7	4.8	6.0
Improvement	72.0	92.8	90.4	76.0
Therapy favorable	94.0	95.5	95.2	82.0
safety (%)				
Mortality	2.0	1.8	0.0	0.0
MB	0.0	0.0	0.0	0.0
CRNMB	2.0	2.7	4.8	10.0
VTE off-treatment	2.0	2.7	0.0	8.0
Therapy unfavorable	6.0	4.5	4.8	18.0

MB, major bleeding; CRNMB, clinically relevant non-major bleeding; VTE, venous thromboembolism. API, apixaban; RIV, rivaroxaban; DAB, dabigatran; LMWH/VKA, low molecular weight heparin followed by vitamin K antagonist.

patients who dropped out of the study were excluded. The data were retrospectively collected from the medical records of 231 patients who received four therapies. The characteristics of the patients are shown in **Table 2**. According to the hospitalization records of the EMR (**Table 3**), the effective rate of treatment and the incidence of the adverse reactions were calculated as shown in **Table 4**. In this primarily included cohort, patients in the VKA group were younger but had higher unfavorable therapy rate. The drug acquisition cost of API was higher than that of others (US$39.47/2.5 mg), and VKA was the

TABLE 5 | Base-case results.

	C	E	CER	ICER	Special
API	5,877.399	0.940	6,252.553	−187017.543	-
RIV	3,072.136	0.955	3,216.897	-	dominant
DAB	3,926.160	0.952	4,124.119	−284674.922	-
VKA	4,325.386	0.820	5,274.862	−9,283.339	-

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CER, the cost-effectiveness ratio; API, apixaban; RIV, rivaroxaban; DAB, dabigatran; LMWH/VKA, low molecular weight heparin followed by vitamin K antagonist.

lowest (US$0.18/2.5 mg) (**Supplementary Table S1**). However, the monitoring cost and the cost of blood tests with intravenous injections which were included the therapy fee (US$2056.08), made the total cost of VKA not the lowest of the four treatment options.

Cost-effectiveness analysis results are shown in **Table 5**. The lowest ICER group was selected as the baseline group to calculate the ICER. In the base case, the RIV group resulted in a mean VTE attributable to 95% effective treatment. The API, DAB, and VKA have a negative ICER value (−187017.543, −284,674.922, and −9,283.339, respectively) and are absolutely inferior solutions.

Markov Results

The cost-effectiveness values of the four regimens simulated by the Markov model after 30 years of treatment of VTE are shown in **Table 6**. The transition probability is shown in **Supplementary Table S2**. Compared with RIV, API was dominant in cost-effectiveness. The DAB and VKA strategy resulted in a slight increase in QALY (0.154 QALYs and 0.146 QALYs, respectively), and the corresponding increase in costs of $17031.885 and $122179.566 resulted in ICERs of $110577.872 per QALY and $836846.343per QALY, respectively. The incremental analysis results of DAB and VKA versus RIV exceeded the threshold range, which proved that DAB and VKA are not economical compared with RIV.

Sensitivity Analysis

One-way sensitivity analysis was performed using key parameters in the model, including cost and utility value, to assess the robustness of the model (**Figure 2**). The following factors including costs of the treatment of DAB, time discounting, the costs of the off-treatment using DAB, the costs of CRNMB of RIV, and the costs of MB using DAB have a significant influence on the result. One-way sensitivity analysis was conducted for the five most influential variables separately. RIV is still the most economically advantageous within the range of changes in sensitivity parameters. (**Supplementary Table S3**). Therefore, it can be inferred that changes in these two variables have no significant effect on the economic advantages of RIV.

Cost-effectiveness acceptability curves (CEAC) are shown in **Figure 3**. Within the threshold range selected, RIV has more economic benefits. RIV has a 100% probability of being cost-effective compared with other regimens when the willingness to pay (WTP) sis $10973 per QALY. When WTP exceeds US$148,000, DAB is more cost-effective than RIV.

One thousand iterations of Monte Carlo simulation methods to further explore the parameter uncertainty are presented in

TABLE 6 | Cost-effectiveness results of Markov model.

Strategy	Cost	Incremental cost	QALY	Incremental QALY	ICER	CER	Special
RIV	6,520.280	0	4.762	0.000	0	1,369.351	-
API	14,569.168	8,048.888	4.724	−0.037	−216176.977	3,083.846	Dominated
DAB	23,552.165	17,031.885	4.916	0.154	110,577.872	4,791.302	-
VKA	128,699.846	105,147.681	4.908	0.146	836,846.343	26,220.793	-

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; CER, the cost-effectiveness ratio.

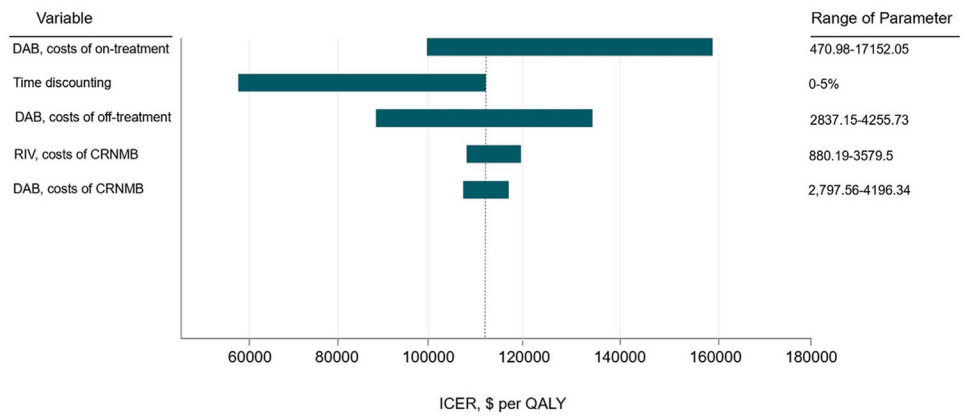

FIGURE 2 | One-way sensitivity analysis tornado diagram.

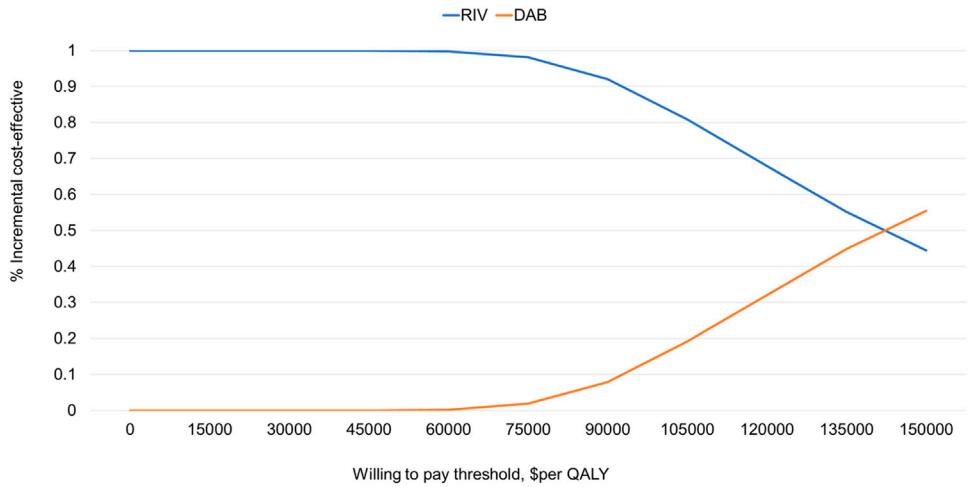

FIGURE 3 | Cost-effectiveness acceptability curves.

Figure 4. The scattered points were distributed more concentratedly inside the ellipse, indicating that the ICER analysis results of the scheme are relatively stable. The ICER for DAB versus RIV (**Figures 4A**) and VKA versus RIV (**Figures 4B**) was greater than $10973.0 per QALY for VTE patients.

DISCUSSION

This study conducted a pharmacoeconomic evaluation for VTE patients using DOACs and VKA standard therapy. RIV was dominant over the short-term hospitalization period. The Markov results we developed as part of the appraisal process verified this conclusion. We estimated that DAB was cost-effective compared with RIV when assuming a WTP threshold of $148000 per QALY in the exploratory analysis of the Markov model.

Our research has several advantages. Few economic evaluations have compared currently approved DOACs with LMWH + VKA for the treatment of VTE patients, especially in China. This study is, to our knowledge, the first research that compared the four therapies simultaneously. Two health outcomes, treatment effectiveness and QALY, were evaluated to determine the conclusion. The study complements the problem that RCT data are based on specific patient populations and specific study settings which may not truly reflect the actual health-care environment. Patients treated with RIV had the highest treatment favorable rate, which may be one of the reasons why RIV has the most economic advantage in clinical treatment. In addition, the model uncertainty was evaluated by using sensitivity analysis parameters.

Our research results have some differences and innovations from previous literature. In line with previous studies, Craig (Seaman et al., 2013) and Li Yang (Yang and Wu, 2020) examined the cost-effectiveness analysis of RIV for VTE treatment versus enoxaparin, which showed that RIV was a cost-effective therapy. However, Abdullah (Al Saleh et al., 2017) suggested that API was likely cost-effective for treatment durations of 3, 6, and 12 months versus DOAC. A study by Amin et al. (2016) found that this distinction probably stems from the fact that a vast majority of this study used EMR data, rather than using the parameters obtained by literature research like other studies. In addition, the definition of MB was slightly different in the respective literature. A study by Peter et al. (2016) divided massive bleeding into fatal MB and non-fatal intracranial bleeding.

The results of one-way sensitivity analysis found that the cost of on-treatment in DAB had the greatest impact on the model outcome. However, after calculating the range of upper and lower limits separately, RIV is still the most cost-effective, and the model is robust. The probability of choosing DAB gradually increases when the patient's willingness-to-pay value exceeds $148,000. Especially, the results are meaningful for the Chinese health-care system, hospitals, and payers. In the case of the same curative effect, doctors can choose the most reasonable therapy according to the economic status of patients. Accounting for the increase in costs and ICER, the addition of VKA and DAB treatment was not an economically viable treatment option for VTE. Although lower price assumptions may not influence the overall cost-effectiveness results, further reductions such as social assistance or medical insurance may contribute to making DAB more affordable for VTE patients (Zhao et al., 2018).

Considering the disadvantage of API, the following facts may provide some explanations. API has a significant effect in reducing the risk of MB, and its safety and effectiveness are beyond those of similar drugs (Baber et al., 2014). But given the high price of API and the foreign patents that have not expired until 2023 (Tichy et al., 2021), the application scale of apixaban is still very rare in China (Yu et al., 2020). It is worth noting that with the launch of generic drugs in China, the reduction of the price of apixaban will lead to a more large-scale application, which probably makes it more economic.

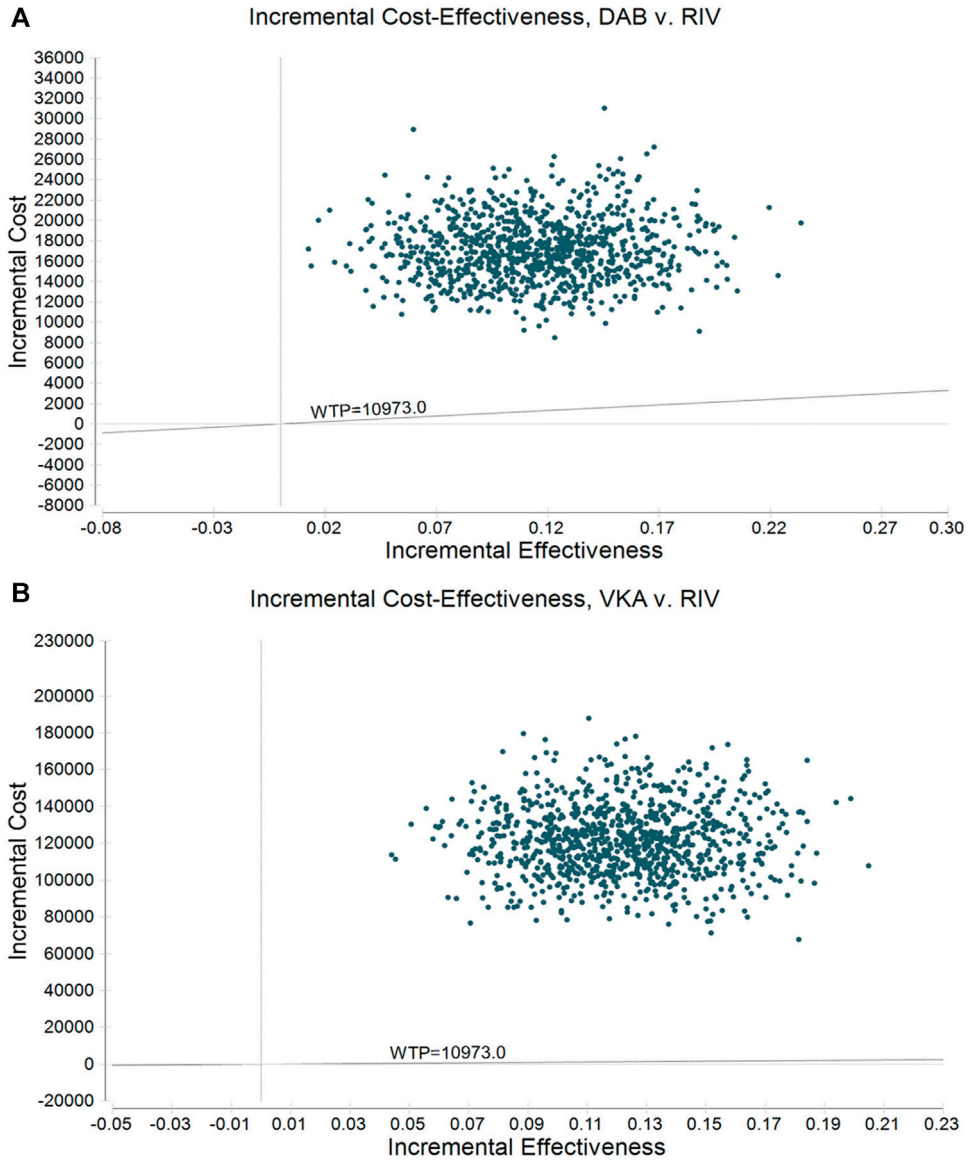

FIGURE 4 | Incremental cost-effectiveness scatter plot of probabilistic sensitivity analysis. **(A)** Dabigatran vs. rivaroxaban; **(B)** LMWH + VKA vs. rivaroxaban.

Limitations

First, the acquisition of transition probability parameters may have a certain impact on the research results. The parameters of the Markov model established in this study were derived from EMR and published literature. The model assumes that the transition probability was a fixed value. In contrast, the transition probability changes with time in the actual treatment process, which causes a certain bias in the model. Therefore, large-scale prospective studies should be used to reduce the resulting bias caused by the transition probability.

Second, another limitation in costs involves the process of collecting cost data. This study adopted the perspective of the health-care system for analysis. Although the complications may result in loss of work expenses and escort expenses for other members of the family, this part of the expenses is difficult to measure in actual follow-up, and it was not included in the study. Moreover, the patient's mental loss due to illness was not included in the study, so the lack of indirect costs and hidden costs resulted in underestimation of the costs of the therapies to a certain extent. However, due to the small difference between the indirect costs and hidden costs of the four schemes, the impact on the results was little. In addition, this study conducted a sensitivity analysis on the cost of each health state of VTE and did not find any difference. Simultaneously, there are some uncertainties and limitations that arise from the use of EMR for cost-effectiveness analysis. For example, it cannot be determined that the patient was

affected by other drugs during drug treatment. The confounding factors and bias of the data also need to be accurately analyzed.

Third, the health utility value obtained from the published literature could not accurately reflect the clinical effect on Chinese patients. Currently, there is no research on the utility value of VTE patients in China, so the utility value data caused by complications in this study refers to the assumptions of similar studies in the model. Due to differences in the level of economic development of different countries, there will be differences in health utility values (Locadia et al., 2004; Mccullagh et al., 2012). However, the sensitivity analysis results of this study suggest that this indicator has little effect on the results.

Fourth, although prolonging the time of anticoagulation therapy can reduce the recurrence rate of VTE by more than 80% (Couturaud et al., 2019; Wang et al., 2018), it does not reduce the risk of recurrence after patients stop using anticoagulant drugs. Since the Markov model simplifies the course of the disease, it will bias the results.

Fifth, in the results of patient data collection, 98% of the patient population treated with API has DVT, which can lead to the occurrence of confounding factors. On the one hand, physicians may adopt different treatment strategies for different disease types On the other hand, DVT patients are prone to post-thrombotic syndrome (Kahn, 2016), which is an important chronic complication of DVT and affects the results. The RIV group is quite older, is heavier, and has fewer females than all other groups. This would cause deviations because obesity, gender, and age can affect physicians' choice of anticoagulant drugs (Mitchell and Conway, 2014; Loffredo et al., 2016; Perales et al., 2020).

Finally, this study did not conduct a subgroup analysis. In fact, in certain patient groups such as pregnant women, cancer patients, and elderly patients, the treatment of VTE is more challenging than the general population (Johannes et al., 2015; Boon et al., 2018). The anticoagulation treatment for specific populations needs to be carefully considered.

In summary, this study found that RIV is the most cost-effective treatment option in the treatment of VTE patients. Due to the limitations of the study, a large-scale prospective study of Chinese patients is still needed to confirm the results of economic evaluation.

CONCLUSION

Short-term inpatient economic evaluation and Markov modeling suggest that relative to LMWH + VKA, DAB, and API, RIV could be considered as a more cost-effective or cost-saving long-term strategy for VTE patients in China. Nevertheless, further evidence is needed using data from large-scale studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the original data is confidential. Requests to access the datasets should be directed to K-XS, 18851101027@163.com

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Xijing Hospital Institutional Review Board (KY20212011-C-1). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

K-XS and YD conceived the study. S-SC, FY, R-YX, and YD contributed toward the intellectual conception of the review, R-YX, Q-XH, and BC extracted and analyzed the data; K-XS and BC wrote the first draft of the article; W-JW, J-WW, and YD revised the article; FY and J-WW supervised the study and contributed to writing the article.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Al Saleh, A. S., Berrigan, P., Anderson, D., and Shivakumar, S. (2017). Direct Oral Anticoagulants and Vitamin K Antagonists for Treatment of Deep Venous Thrombosis and Pulmonary Embolism in the Outpatient Setting: Comparative Economic Evaluation. *Can. J. Hosp. Pharm.* 70, 188–199. doi:10.4212/cjhp.v70i3.1658

Amin, A., Bruno, A., Trocio, J., Lin, J., Lingohr-Smith, M. J. C., and Hemostasis, A. T. (2016). Real-World Medical Cost Avoidance when New Oral Anticoagulants Are Used versus Warfarin for Venous Thromboembolism in the United States. *Clin. Appl. Thromb. Hemost. 22*, 5–11. doi:10.1177/1076029615585991

Angchaisuksiri, P., Goto, S., Farjat, A., Fryk, H., Bang, S., Chiang, C., et al. (2021). Venous Thromboembolism in Asia and Worldwide: Emerging Insights from GARFIELD-VTE. 201, 6372. doi:10.1016/j.thromres.2021.02.024

Baber, U., Mastoris, I., and Mehran, R. (2014). Balancing Ischaemia and Bleeding Risks with Novel Oral Anticoagulants. *Nat. Rev. Cardiol.* 11, 693–703. doi:10.1038/nrcardio.2014.170

Barco, S., Mahmoudpour, S. H., Valerio, L., Klok, F. A., Münzel, T., Middeldorp, S., et al. (2020). Trends in Mortality Related to Pulmonary Embolism in the European Region, 2000-15: Analysis of Vital Registration Data from the WHO Mortality Database. *Lancet Respir. Med.* 8, 277–287. doi:10.1016/S2213-2600(19)30354-6

Boon, G. J. A. M., Van Dam, L. F., Klok, F. A., and Huisman, M. V. (2018). Management and Treatment of Deep Vein Thrombosis in Special Populations. *Expert Rev. Hematol.* 11, 685–695. doi:10.1080/17474086.2018.1502082

Briggs, A., and Sculpher, M. (1998). An Introduction to Markov Modelling for Economic Evaluation. *Pharmacoeconomics* 13, 397–409. doi:10.2165/00019053-199813040-00003

Chopard, R., Albertsen, I. E., and Piazza, G. (2020). Diagnosis and Treatment of Lower Extremity Venous Thromboembolism: A Review. *JAMA* 324, 1765–1776. doi:10.1001/jama.2020.17272

Couturaud, F., Pernod, G., Presles, E., Duhamel, E., Jego, P., Provost, K., et al. (2019). Six Months versus Two Years of Oral Anticoagulation after a First Episode of Unprovoked Deep-Vein Thrombosis. *Haematologica* 104, 1493–1501. doi:10.3324/haematol.2018.210971

Cushman, M., Barnes, G. D., Creager, M. A., Diaz, J. A., Henke, P. K., Machlus, K. R., et al. (2020). Venous Thromboembolism Research Priorities: A Scientific Statement from the American Heart Association and the International Society on Thrombosis and Haemostasis. *Circulation* 142, e85–94. doi:10.1161/CIR.0000000000000818

Di Nisio, M., Van Es, N., Büller, H. R., and London, R. J. L. (2016). Deep Vein Thrombosis and Pulmonary Embolism. *Lancet* 388, 3060–3073. doi:10.1016/S0140-6736(16)30514-1

Gage, B. F., Cardinalli, A. B., and Owens, D. K. (1996). The Effect of Stroke and Stroke Prophylaxis with Aspirin or Warfarin on Quality of Life. *Arch. Intern. Med.* 156, 1829–1836. doi:10.1001/archinte.156.16.1829

Gould, M., Garcia, D., Wren, S., Karanicolas, P., Arcelus, J., Heit, J., et al. (2012). Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis. *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. 9th ed, 141, 227S–277S. doi:10.1378/chest.141.5.1369b

Guo, R. (2020). *Government of China Ethnic Statistical Yearbook 2020*. Beijing: National Bureau of Statistics. Available at: https://datascience.shanghai.nyu.edu/datasets/national-bureau-statistics-china.

Hogg, K., Kimpton, M., Carrier, M., Coyle, D., Forgie, M., and Wells, P. (2013). Estimating Quality of Life in Acute Venous Thrombosis. *JAMA Intern. Med.* 173, 1067–1072. doi:10.1001/jamainternmed.2013.563

Howard, L. S., and Hughes, R. J. (2013). NICE Guideline: Management of Venous Thromboembolic Diseases and Role of Thrombophilia Testing. *Thorax* 68, 391–393. doi:10.1136/thoraxjnl-2012-202376

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., et al. (2013). Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and Elaboration: a Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 16, 231–250. doi:10.1016/j.jval.2013.02.002

Johannes, T., Ingrid, P., and Cihan, A. (2015). Anticoagulant Treatment of Deep Vein Thrombosis and Pulmonary Embolism: The Present State of the Art. 2, 30. doi:10.3389/fcvm.2015.00030

Kaatz, S., Ahmad, D., Spyropoulos, A. C., and Schulman, S. Subcommittee on Control of Anticoagulation (2015). Definition of Clinically Relevant Non-major Bleeding in Studies of Anticoagulants in Atrial Fibrillation and Venous Thromboembolic Disease in Non-surgical Patients: Communication from the SSC of the ISTH. *J. Thromb. Haemost.* 13, 2119–2126. doi:10.1111/jth.13140

Kahn, S. R. (2016). The post-thrombotic Syndrome. *Hematol. Am Soc Hematol Educ Program* 2016, 413–418. doi:10.1182/asheducation-2016.1.413

Kakkos, S. K., Gohel, M., Baekgaard, N., Bauersachs, R., Bellmunt-Montoya, S., Black, S. A., et al. (2021). Editor's Choice - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. *Eur. J. Vasc. Endovasc Surg.* 61, 9–82. doi:10.1016/j.ejvs.2020.09.023

Kong, C. Y., Mcmahon, P. M., and Gazelle, G. S. (2009). Calibration of Disease Simulation Model Using an Engineering Approach. *Value Health* 12, 521–529. doi:10.1111/j.1524-4733.2008.00484.X

López-López, J., Sterne, J. A., Thom, H., Higgins, J., Hingorani, A. D., Okoli, G. N., et al. (2017). Oral Anticoagulants for Prevention of Stroke in Atrial Fibrillation: Systematic Review, Network Meta-Analysis, and Cost-Effectiveness Analysis. doi:10.1136/bmj.j5058

Lanitis, T., Leipold, R., Hamilton, M., Rublee, D., Quon, P., Browne, C., et al. (2016). Cost-effectiveness of Apixaban versus Other Oral Anticoagulants for the Initial Treatment of Venous Thromboembolism and Prevention of Recurrence. *Clin. Ther.* 38, 478–493.e1–e16. doi:10.1016/j.clinthera.2016.01.020

Lee, L. H., Gallus, A., Jindal, R., Wang, C., and Wu, C. C. (2017). Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review. *Thromb. Haemost.* 117, 2243–2260. doi:10.1160/TH17-02-0134

Li: Qy, L., Yc, L., and Zhang, Y. Q. (2015). Analysis of Clinical Data of 1136 Inpatients with Venous Thromboembolism in 2003-2013. *J. Pract. Med.* 6, 1006–1008.

Liu, G., Hu, S., Wu, J., Wu, J., Yang, L., and Li, H. (2015). *China Guidelines for Pharmacoeconomic Evaluations*. China.

Locadia, M., Bossuyt, P. M. M., Stalmeier, P. F. M., Sprangers, M. A. G., van Dongen, C. J. J., Middeldorp, S., et al. (2004). Treatment of Venous Thromboembolism with Vitamin K Antagonists: Patients' Health State Valuations and Treatment Preferences. *Thromb. Haemost.* 92, 1336–1341. doi:10.1160/TH04-02-0075

Loffredo, L., Violi, F., and Perri, L. (2016). Sex Related Differences in Patients with Acute Venous Thromboembolism Treated with New Oral Anticoagulants. A Meta-Analysis of the Interventional Trials. *Int. J. Cardiol.* 212, 255–258. doi:10.1016/j.ijcard.2016.03.086

Mccullagh, L., Walsh, C., and Barry, M. (2012). Value-of-Information Analysis to Reduce Decision Uncertainty Associated with the Choice of Thromboprophylaxis after Total Hip Replacement in the Irish Healthcare Setting. *Pharmacoeconomics* 30, 941–959. doi:10.2165/11591510-000000000-00000

Mitchell, A. P., and Conway, S. E. (2014). Rivaroxaban for Treatment of Venous Thromboembolism in Older Adults. *Consult Pharm.* 29, 627–630. doi:10.4140/TCP.n.2014.627

Naimark, D. M., Bott, M., and Krahn, M. (2008). The Half-Cycle Correction Explained: Two Alternative Pedagogical Approaches. *Med. Decis. Making* 28, 706–712. doi:10.1177/0272989X08315241

Nemeth, B., Lijfering, W. M., Nelissen, R. G. H. H., Schipper, I. B., Rosendaal, F. R., Le Cessie, S., et al. (2019). Risk and Risk Factors Associated with Recurrent Venous Thromboembolism Following Surgery in Patients with History of Venous Thromboembolism. *JAMA Netw. Open* 2, e193690. doi:10.1001/jamanetworkopen.2019.3690

Ortel, T. L., Neumann, I., Ageno, W., Beyth, R., Clark, N. P., Cuker, A., et al. (2020). American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism - ScienceDirect. *Blood Adv.* 4, 4693–4738. doi:10.1182/bloodadvances.2020001830

Paulden, M., O'Mahony, J. F., and Mccabe, C. (2017). Discounting the Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine. *Pharmacoeconomics* 35, 5–13. doi:10.1007/s40273-016-0482-0

Perales, I. J., San Agustin, K., Deangelo, J., and Campbell, A. M. (2020). Rivaroxaban versus Warfarin for Stroke Prevention and Venous Thromboembolism Treatment in Extreme Obesity and High Body Weight. *Ann. Pharmacother.* 54, 344–350. doi:10.1177/1060028019886092

Peter, Q., Le, H. H., Raymond, V., Mtibaa, M., and Economics, A. (2016). Clinical and Economic Benefits of Extended Treatment with Apixaban for the Treatment and Prevention of Recurrent Venous Thromboembolism in Canada. *J. Med. Econ.* 19, 557–567. doi:10.3111/13696998.2016.1141780

Petitti, D. B. (2002). *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis*. Oxford University Press.

Raskob, G. E., Angchaisuksiri, P., Blanco, A. N., Buller, H., Gallus, A., Hylek, B. J. E. M., et al. (2014). Thrombosis: a Major Contributor to Global Disease burden.

Arterioscler Thromb. Vasc. Biol. 34, 2363–2371. doi:10.1161/ATVBAHA.114.304488

Renner, E., and Barnes, G. D. (2020). Antithrombotic Management of Venous Thromboembolism: JACC Focus Seminar. *J. Am. Coll. Cardiol.* 76, 2142–2154. doi:10.1016/j.jacc.2020.07.070

Sanson-Fisher, R. W., Bonevski, B., Green, L. W., and D'este, C. (2007). Limitations of the Randomized Controlled Trial in Evaluating Population-Based Health Interventions. *Am. J. Prev. Med.* 33, 155–161. doi:10.1016/j.amepre.2007.04.007

Schulman, S., and Kearon, C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (2005). Definition of Major Bleeding in Clinical Investigations of Antihemostatic Medicinal Products in Non-surgical Patients. *J. Thromb. Haemost.* 3, 692–694. doi:10.1111/j.1538-7836.2005.01204.x

Schulman, S., Konstantinides, S., Hu, Y., and Tang, L. V. (2020). Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing: Observations on NICE Guideline [NG158]. *Thromb. Haemost.* 120, 1143–1146. doi:10.1055/s-0040-1712913

Seaman, C. D., Smith, K. J., and Ragni, M. V. (2013). Cost-effectiveness of Rivaroxaban versus Warfarin Anticoagulation for the Prevention of Recurrent Venous Thromboembolism: A U.S. Perspective. *Thromb. Res.* 132, 647–651. doi:10.1016/j.thromres.2013.09.015

Tichy, E., Hoffman, J., Suda, K., Rim, M., Tadrous, M., Cuellar, S., et al. (2021). National Trends in Prescription Drug Expenditures and Projections for 2021. *Am. J. Health Syst. Pharm.* 78, 1294–1308. doi:10.1093/ajhp/zxab160

Wang, K. L., van Es, N., Cameron, C., Castellucci, L. A., Büller, H. R., and Carrier, M. (2018). Extended Treatment of Venous Thromboembolism: A Systematic Review and Network Meta-Analysis. *Heart* 105, 545–552. doi:10.1136/heartjnl-2018-313617

Wang Sheng-Xiang, R. Y.-P., Nan, Li., Dou, Ni-Na., Wang, Qian., Lu, Shan., and Zhao, Ke-Xin. (2020). Cost-effectiveness Evaluation of Apixaban, rivaroxaban, dabigatran, enoxaparin in the Prevention of Venous Thromboemblism after Total Hip and Knee Arthroplasty. *Chin. J. Hosp. Pharm.* 40, 2.,No.

Weinstein, M. C., O'brien, B., Hornberger, J., Jackson, J., Johannesson, M., Mccabe, C., et al. (2010). Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health* 6, 9–17. doi:10.1046/j.1524-4733.2003.00234.x

World Health Organization (2003). WHO Guide to Cost-Effectiveness Analysis. Available at: https://www.who.int/choice/publications/p_2003_generalised_cea.pdf (Accessed August 1, 2020).

Wu, B., Li, K., Liu, X., and He, B. (2014a). Cost-effectiveness of Different Strategies for Stroke Prevention in Patients with Atrial Fibrillation in a Health Resource-Limited Setting. *Cardiovasc. Drugs Ther.* 28, 87–98. doi:10.1007/s10557-013-6490-9

Wu, C., Alotaibi, G. S., Alsaleh, K., and Sean Mcmurtry, M. (2014b). Case Fatality of Bleeding and Recurrent Venous Thromboembolism during, Initial Therapy with Direct Oral Anticoagulants: a Systematic Review. *Thromb. Res.* 134, 627–632. doi:10.1016/j.thromres.2014.07.001

Yan, X., Gu, X., Xu, Z., Lin, H., and Wu, B. (2016). Cost-Effectiveness of Different Strategies for the Prevention of Venous Thromboembolism after Total Hip Replacement in China. *Adv. Ther.* 34, 466–480. doi:10.1007/s12325-016-0460-0

Yang, L., and Wu, J. (2020). Cost-effectiveness of Rivaroxaban Compared with Enoxaparin Plus Warfarin for the Treatment of Hospitalised Acute Deep Vein Thrombosis in China. *BMJ Open* 10, e038433. doi:10.1136/bmjopen-2020-038433

Yu, Z., Yu, L., and Shan, C. (2020). Trends of Ambulatory Oral Anticoagulant Prescription in Five Major Cities of China, 2012-2017. *BMC Health Serv. Res.* 20, 209–2017. doi:10.1186/s12913-020-5072-3

Zhai, Z., Kan, Q., Li, W., Qin, X., Qu, J., Shi, Y., et al. (2019). VTE Risk Profiles and Prophylaxis in Medical and Surgical Inpatients: The Identification of Chinese Hospitalized Patients' Risk Profile for Venous Thromboembolism (DissolVE-2)-A Cross-Sectional Study. *Chest* 155, 114–122. doi:10.1016/j.chest.2018.09.020

Zhang, Z., Lei, J., Shao, X., Dong, F., Wang, J., Wang, D., et al. (2019). Trends in Hospitalization and In-Hospital Mortality from VTE, 2007 to 2016, in China. *Chest* 155, 342–353. doi:10.1016/j.chest.2018.10.040

Zhao, X., Cui, X. Y., Han, Y., and Pharmacy, D. O. J. D. E. (2018). *The Coverage of Primary Medical Insurance in Individual Municipalities and Provinces for New Oral Anticoagulants*.

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Cost-Effectiveness of Adding SGLT2 Inhibitors to Standard Treatment for Heart Failure With Reduced Ejection Fraction Patients in China

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Objective: To evaluate the economics and effectiveness of adding dapagliflozin or empagliflozin to the standard treatment for heart failure (HF) for patients with reduced ejection fraction (HFrEF) in China.

Methods: A Markov model was developed to project the clinical and economic outcomes of adding dapagliflozin or empagliflozin to the standard treatment for 66-year-old patients with HFrEF. A cost-utility analysis was performed based mostly on data from the empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) study and the dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF) trial. The primary outcomes were measured *via* total and incremental costs and quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER).

Results: In China, compared to the standard treatment, although adding dapagliflozin to the standard treatment in the treatment of HFrEF was more expensive ($4,870.68 vs. $3,596.25), it was more cost-effective (3.87 QALYs vs. 3.64 QALYs), resulting in an ICER of $5,541.00 per QALY. Similarly, adding empagliflozin was more expensive ($5,021.93 vs. $4,118.86) but more cost-effective (3.66 QALYs vs. 3.53 QALYs), resulting in an ICER of $6,946.69 per QALY. A sensitivity analysis demonstrated the robustness of the model in identifying cardiovascular death as a significant driver of cost-effectiveness. A probabilistic sensitivity analysis indicated that when the willingness-to-pay was $11,008.07 per QALY, the probability of the addition of dapagliflozin or empagliflozin being cost-effective was 70.5 and 55.2%, respectively. A scenario analysis showed that the cost of hospitalization, diabetes status, and time horizon had a greater impact on ICER.

Conclusion: Compared with standard treatments with or without empagliflozin, adding dapagliflozin to the standard treatment in the treatment of HFrEF in China was extremely cost-effective.

Keywords: dapagliflozin, empagliflozin, heart failure, cost-effectiveness analysis, China

INTRODUCTION

Heart failure (HF) is a serious clinical manifestation or a terminal stage of various heart diseases and has become an increasingly serious global public health problem (Conrad et al., 2018; Gu et al., 2003). In recent years, the prevalence of HF in China has increased to approximately 2%, and there are approximately 8–10 million patients experiencing HF (The US Centers for Disease Control and Prevention, 2016). It was estimated that the total direct and indirect costs related to HF in China in 2012 were approximately $0.84 billion (Cook et al., 2014), which would add a huge economic burden to China's medical security system. Although great progress has been made in the field of HF treatment in the past 30 years, the 5-years mortality rate remains as high as 50%, and more than 50% of discharged patients will need to be hospitalized again within the next 6 months (Virani et al., 2020; Desai and Stevenson, 2012).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been developed as a new therapeutic agent for the treatment of type 2 diabetes mellitus (T2DM), which can inhibit the proximal renal tubular SGLT protein family reabsorption of glucose, thereby reducing blood sugar levels (Chao and Henry, 2010). Notably there are some mechanisms pertaining to their cardiovascular (CV) benefits independently of blood glucose regulation, including natriuresis, increasing circulating ketone levels, anti-inflammatory effects, and reducing sympathetic overactivity (Andreadou et al., 2020; Iorga et al., 2020; Lymperopoulos et al., 2021). In particular, SGLT2 inhibitors better explain the left ventricle (LV) systolic function by improving cardiac energetics and reversing remodeling with reduction in LV volumes and LV mass (Garcia-Ropero et al., 2019; Jensen et al., 2020). SGLT2 inhibitors also improve LV diastolic function by reducing congestion and cardiac filling pressures (Santos-Gallego et al., 2021; Requena-Ibanez et al., 2021). Some studies have found that SGLT2 inhibitors regress interstitial myocardial fibrosis, reduce epicardial adipose tissue, and improve aortic stiffness (Nassif et al., 2021). The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) study and the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study found that both dapagliflozin and empagliflozin can reduce the risk of CV death or hospitalization in HFrEF patients with or without T2DM (Mcmurray et al., 2019; Packer et al., 2020). The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) study found that empagliflozin could also be effective for heart failure with preserved ejection fraction (HFrEF) (Anker S. D. et al., 2021). Also, the United States Food and Drug Administration (FDA) announced that dapagliflozin and empagliflozin could be used for the treatment of HFrEF.

However, adding SGLT2 inhibitors to standard treatment in the treatment of HFrEF in China will significantly increase the cost of treatment. Several studies have been conducted in numerous European countries—including Thailand, Australia, and other countries to evaluate the cost-effectiveness of SGLT2 inhibitors for HFrEF (Mcewan et al., 2020; Savira et al., 2021; Krittayaphong and Permsuwan, 2021), but the medical systems and economic status of these countries are different from those of China. Therefore, it is essential to evaluate the economic impact among Chinese patients to guide clinicians and decision-makers to determine the best value of this new treatment option. Therefore, our study aimed to examine the cost-effectiveness of adding dapagliflozin or empagliflozin to the standard treatment of HFrEF in China.

METHODS AND MATERIAL

Module Building

We constructed a Markov model for cost-utility analysis to compare the economics of three standard treatment options: standard treatment; adding dapagliflozin (10 mg, once daily) to the standard treatment; and adding empagliflozin (10 mg, once daily) to standard treatment. Based on the characteristics of the natural course of HFrEF and the availability of inter-state transition probability, this study set HFrEF patients into the following five states: New York Heart Association (NYHA) function classifications I, II, III, and IV and death, among which the death state was in the absorption state (Wu et al., 2020). Since the risk of readmission in the vulnerable period of HF was much higher than that in the stable period (Greene et al., 2015), we assumed that in our model, all patients who had experienced high-frequency hospitalizations had HF readmissions within 3 months. So, we arranged a fixed probability of readmission for each HF; at the end of each cycle, the patient switched between different NYHA function classifications. Events included hospitalization for HF, readmission for HF, CV death, and non-CV death. The patient can transfer between the states by pressing the arrow, as shown in **Figure 1**.

According to the EMPEROR-Reduced study and the DAPA-HF study, the inclusion criteria in our model were as follows: 1) age >18 years and diagnosis of HFrEF (NYHA II-IV) over 2 months; 2) LVEF ≤40% (LV ejection fraction) within the past 12 months; 3) N-terminal pro-brain natriuretic peptide (NT-proBNP) is elevated; and 4) receiving standard treatment for HFrEF, including drugs and medical devices. The exclusion criteria were as follows: 1) recently taking or tolerating SGLT2 inhibitors; 2) hypotension or systolic blood pressure below 95 mmHg; 3) type I diabetes; and 4) glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 (or rapid decline in renal function). The average age of the study population was 66 years. According to the natural outcome of the disease and the expected survival period of the population in this study, the model will be run for 10 years, with a period of 3 months (90 days), which is 40 cycles. According to the recommendations of the Chinese Pharmacoeconomic Evaluation Guide 2019 (Research Group of China Pharmacoeconomics Evaluation 2019), all costs and utilities were discounted at an annual discount rate of 5%, and sensitivity analysis was performed between 0 and 8%. Our model used a half-period correction to prevent the overestimation of the expected survival time.

In the real world, the process of disease development, diagnosis, and treatment is more complicated, so some assumptions are needed in the model simulation to make the model reasonable and simplified. This study proposed the following hypotheses based on the progression of HFrEF and the process of diagnosis and treatment: 1) assuming that all

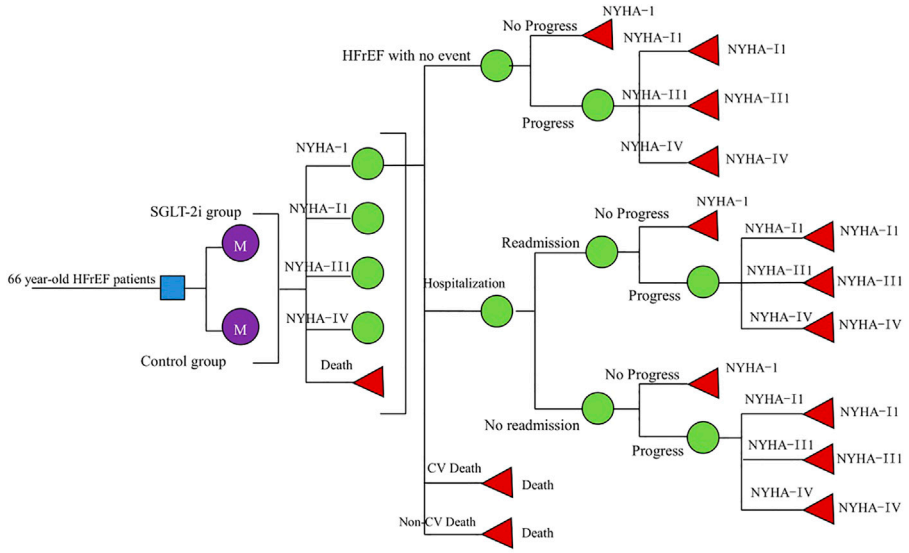

FIGURE 1 | Schematic representation of the Markov model.

patients were in stable HF before entering the long-term Markov model; 2) assuming that the effect of dapagliflozin and empagliflozin on HFrEF would not change with time; and 3) assuming that the probability of each event during 10 years would not be unchanged.

Transition Probability

The initial NYHA function classification distribution in our cohort was derived from the DAPA-HF and the EMPEROR-Reduced studies (0% I, 71.3% II, 28% III, and 0.7% IV). In the DAPA-HF study, over the 18.2-months follow-up period, the rate of cardiovascular mortality (CM) in the dapagliflozin group and Control Group 1 was 9.6 and 11.5%, while the risk of hospitalization for HF was 9.7 and 13.4%,respectively (Mcmurray et al., 2019). During the EMPEROR-Reduced study's 16 months follow-up period, the CM in the empagliflozin group was 10.0% and Control Group 2 was 10.8%, while the risk of hospitalization for HF in the empagliflozin group and Control Group 2 was 13.2 and 18.3%, respectively (Packer et al., 2020). Age-dependent non-CV deaths were all from the Report on China's Cause of Death 2018, which is published by the China Center for disease Control and Prevention (National Center for Chronic and Noncommunicable Disease Control and Prevention, 2019). Furthermore, the readmission rate for HF was based on the literature published by Huang Jun (Huang et al., 2017). Based on the declining exponential approximation of life expectancy (DEALE) principle, the time length was converted into a rate, and then the rate was converted into a transition probability every 3 months (Park et al., 2019) with the following formula:

$$r = -\frac{1}{t}\ln(S)$$

$$P = 1 - e^{-r*T}$$

Among them, S is the rate, t is the time, and P is the transition probability converted into every 3 months. We used the formula to calculate the transition probability of all parameters every 3 months (**Table 1**), and the 3-month transition probability between NYHA function classifications was also provided (King et al., 2016) (**Table 2**).

Cost

From the perspective of the Chinese medical and health system, this study only calculated direct medical costs. The standard treatment cost included angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), beta-blockers, spironolactone, and diuretics from a previous study (Huang et al., 2017). Moreover, we assumed that the standard treatment was $102.75 per cycle, which was converted to $118.95 in 2020 according to the annual discount rate of 5%. Considering that approximately 10% of the DAPA-HF study took sacubitril/valsartan (SAC/VAL) and 19% of the EMPEROR-Reduced study took SAC/VAL, we calculated that the cost of SAC/VAL for 3 months was $556.21 (target dose 200 mg, twice daily). Correspondingly, according to the latest national negotiation price in 2020, enalapril was $0.087 per 10 mg twice daily and SAC/VAL was $3.10 per 200 mg twice daily, so the range of standard treatment costs was calculated (**Table 1**). The cost of hospitalization for HF was from the China Health Statistics Yearbook 2020, which included town-level, county-level, municipal, provincial, and ministerial hospitals. We calculated that hospitalization cost $1,785.36 (Ma, 2020), dapagliflozin was $0.677 per 10 mg daily, and empagliflozin was $0.658 per 10 mg daily according to the latest national negotiation price in 2020; also, the 90-days cost was $60.93 for dapagliflozin and $59.25 for empagliflozin (**Table 1**). All costs were converted at the rate of.

6.44 ¥/USD (The People's Bank of China, 2020).

TABLE 1 | Clinical input parameters.

Parameters	Value	Range	Distribution	Reference	Notes
Probability of CV mortality					
Dapagliflozin group	0.01650	0.01485–0.01815	Beta	Mcmurray et al. (2019)	±10% of the mean
Control1 group	0.01994	0.01795–0.02193	Beta	Mcmurray et al. (2019)	±10% of the mean
Empagliflozin group	0.01956	0.01760–0.02152	Beta	Packer et al. (2020)	±10% of the mean
Control2 group	0.02120	0.01908–0.02332	Beta	Packer et al. (2020)	±10% of the mean
Probability of HF hospitalization					
Dapagliflozin group	0.01668	0.0150–0.01835	Beta	Mcmurray et al. (2019)	±10% of the mean
Control1 group	0.02344	0.02110–0.02578	Beta	Mcmurray et al. (2019)	±10% of the mean
Empagliflozin group	0.02619	0.02357–0.02881	Beta	Packer et al. (2020)	±10% of the mean
Control2 group	0.03719	0.03347–0.04091	Beta	Packer et al. (2020)	±10% of the mean
Probability of non-CV mortality by age					
65–69 years	0.2430%			National Center for Chronic and Noncommunicable Disease Control and Prevention (2019)	Local data
70–74 years	0.3042%			National Center for Chronic and Noncommunicable Disease Control and Prevention (2019)	Local data
75–79 years	0.4185%			National Center for Chronic and Noncommunicable Disease Control and Prevention (2019)	Local data
Probability of HF readmission	0.1189	0.10701–0.13079	Beta	Huang et al. (2017)	±10% of the mean
Utility input					
NYHA I	0.2035	0.19525–0.2125	Beta	King et al. (2016)	95% CI
NYHA II	0.18	0.17325–0.18725	Beta	King et al. (2016)	95% CI
NYHA III	0.1475	0.13775–0.15725	Beta	King et al. (2016)	95% CI
NYHA IV	0.127	0.103–0.15125	Beta	King et al. (2016)	95% CI
Hospitalization and readmission	-0.1	-0.13–-0.08	Beta	King et al. (2016)	95% CI
Cost					
Standard treatment	$118.95	$118.95–556.21	Gammma	Huang et al. (2017)	95% CI
Dapagliflozin	$60.93	$48.74–73.12	Gammma	Local data	±20% of the mean
Empagliflozin	$ 59.25	$47.40–71.10	Gammma	Local data	±20% of the mean
Hospitalization and readmission	$1,785.36	$ 964.07–3209.47	Gammma	Ma, (2020)	Local data
Discounted rate	5%	0–8%		Research group of China Pharmacoeconomics Evaluation (2019)	

Utility

In this study, quality-adjusted life years (QALYs) were used as a measure of effect. The utility of different levels of NYHA function classifications was derived from published literature (**Table 1**), and scores were based on a scale from 0 (death) to 1 (perfect health). NYHA I through IV used a one-time utility of −0.1, for each hospitalization and readmission event (**Table 1**) (King et al., 2016).

Outcome

The primary endpoints in this study were QALY, cost, and the incremental cost-effectiveness ratio (ICER). Notably, the following is according to the recommendation of the World Health Organization (WHO) for the evaluation of pharmacoeconomics (Eichler et al., 2004): ICER <1 fold of gross domestic product (GDP) per capita, the increased cost is completely worth it and very cost-effective; 1 fold of GDP per capita < ICER <3 fold of GDP per capita, the increased cost is acceptable and cost-effective; ICER >3 fold of GDP per capita, the increased cost is not worth it and not cost-effective. According to the data released by the National Bureau of Statistics, per capita GDP in 2019 in China was $11,008.07 (National Bureau of Statistics of the People's Republic of China, 2019). Given this, we used one time per capita GDP ($11,008.07 per QALY) in 2019 as the threshold standard and the willingness-to-pay (WTP) to judge whether a health intervention is cost-effective.

TABLE 2 | New York Heart Association classification transition probabilities per cycle (3 months).

To	I	II	III	IV	Distribution
From					
I	0.977	0.019	0.004	0	Dirichlet
II	0.008	0.981	0.010	0.001	Dirichlet
III	0	0.034	0.960	0.006	Dirichlet
IV	0	0	0.055	0.945	Dirichlet

Sensitivity Analysis

One-way sensitivity was performed to investigate the effects of uncertainty in the model. The model parameters were varied over 95% confidence intervals. Variations of ±10% and ±20% were assumed for parameters of probability and medical costs that have no specified data range (**Table 1**), and the results of each parameter on the ICER are displayed as a tornado diagram.

This study also performed a scenario analysis of diabetes status, hospitalization costs, and time horizon. According to the DAPA-HF and the EMPEROR-Reduced studies, for the non-diabetic and diabetic subgroups, the CM or rehospitalization for HF in the dapagliflozin group or empagliflozin group was lower than that in the control group (Petrie et al., 2020; Anker SD. et al., 2021). There were different levels of hospitals, including town-level hospitals ($964.07); county-level hospitals ($1,120.75); municipal hospitals ($1,785.36); provincial hospitals ($2,812.51); and ministerial hospitals ($3,209.47). The time horizon of 5, 10, 15, and 20 years was also changed to explore its impact on the estimated ICER.

A probabilistic sensitivity analyses (PSA) was also carried out to investigate the uncertainty of all the parameters simultaneously. We assumed that the cost followed the gamma distribution and the utility and the transition probability followed the beta distribution. This was achieved by calculating the results of 1,000 Monte Carlo simulations with different parameter distributions, which were transformed into cost-effectiveness acceptability curves (CEACs).

RESULTS

Model Validation and Clinical Results

The average age of the simulated population in this study was 66 years. Our model predicted that the all-cause mortality at 18 months in the dapagliflozin group was 10.9%, the CM was 9.08%, and the rate of hospitalization for HF was 11.0.%; the all-cause mortality in Control Group 1 was 12.8%, the CM was 10.98%, and the rate of hospitalization for HF was 15.3%; the all-cause mortality at 16 months in the empagliflozin group was 11.6%, the CM was 10.04%, and the rate of hospitalization for HF was 15.5%; the all-cause mortality in Control Group 2 was 12.4%, the CM was 10.84%, and the rate of hospitalization for HF was 22.5%. The median survival time of the dapagliflozin group and Control Group 1 was 8.75 and 7.50 years, respectively; the median survival time of the empagliflozin group and Control Group 2 were 7.5 and 7.25 years, respectively. These median survival times indicated to us that the outcome predicted by our model was close to the results of clinical trials.

Cost-Utility Analysis

The results are presented in **Table 3**. The total utility of the dapagliflozin group after 40 cycles was 3.87 QALYs, which was 0.23 QALYs higher than Control Group 1. The total cost of the dapagliflozin group was $4,870.68, which was $1,274.43 higher than Control Group 1, and the ICER was $5,541.00 per QALY, which was lower than China's per capita GDP of $11,008.07 in 2019. So, this indicated that the dapagliflozin group was more cost-effective. The total utility of the empagliflozin group after 40 cycles was 3.66 QALYs, which was 0.13 QALYs higher than that of Control Group 2 and the total cost of the empagliflozin group was $5,021.93, which was $903.07 higher than that of Control Group 2. Furthermore, the ICER was 6,946.69 per QALY, which was lower than China's per capita GDP of $11,008.07 in 2019. Accordingly, the empagliflozin group was more cost-effective and so the dapagliflozin group had an absolute economic advantage compared with the empagliflozin group.

Sensitivity Analysis

A one-way sensitivity analysis of the dapagliflozin group and Control Group 1 is shown in **Figure 2**. When all parameters changed within the set range of variation, the ICER was within 1 fold per capita GDP, and the one-way sensitivity analysis of the empagliflozin group and Control Group 2 are shown in **Figure 3**. The low value of CM in Control Group 2 and the high value of CM in the empagliflozin group had a greater impact on the results, which was far more than one fold per capita GDP, but other parameters had little impact.

Based on the scenario analysis, in both the dapagliflozin and empagliflozin groups, the ICER of the diabetic group was lower than that of the non-diabetic group; as the cost of hospitalization for different levels of hospitals increased, the ICER gradually decreased, and as the time horizon became longer, the ICER gradually decreased (see **Table 4**).

The CEACs (**Figures 4A,B**) were shown when the WTP was $11,008.07, and the probability that the dapagliflozin and empagliflozin groups were 70.5 and 55.2%, respectively. The results of the PSA based on 1,000 Monte Carlo simulations are presented as a scatter plot (**Figures 5A,B**) where the scattered points were mainly distributed in the first quadrant and most of them were below the WTP threshold line. The PSA results were similar to the basic analysis results; the dapagliflozin group was more cost-effective.

DISCUSSION

This study is the first cost-utility study to add dapagliflozin or empagliflozin to the standard treatment in the treatment of HFrEF in China based on data from the EMPEROR-Reduced and the DAPA-HF studies—as well as China's public databases. Our study showed that compared with standard treatments with or without empagliflozin, adding dapagliflozin to the standard treatment in the treatment of HFrEF in China was extremely cost-effective. The ICER was $5,541 per QALY, which was lower than China's per capita GDP of $11,008.07 in 2019. According to our model, it is assumed that 10 million HF patients will be treated with dapagliflozin in the standard treatment, which reduces 300,000 hospitalizations for HF and 180,000 deaths. The

TABLE 3 | The results from base-case analysis.

	Total cost ($)	Total life years (QALY)	Incremental cost ($)	Incremental life years (QALY)	ICER($ per QALY)
Dapagliflozin group	4,870.68	3.87	1,274.43	0.23	5,541.00
Control1 group	3,596.25	3.64			
Empagliflozin group	5,021.93	3.66	903.07	0.13	6,946.69
Control2 group	4,118.86	3.53			

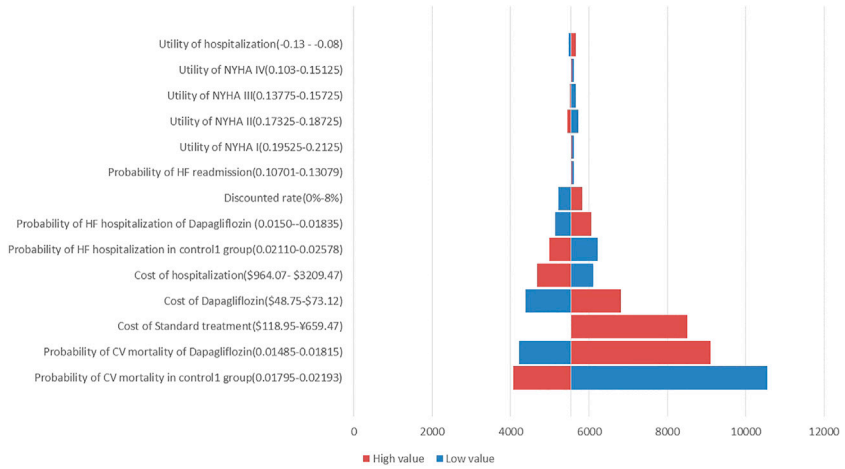

FIGURE 2 | Tornado diagram showing the univariate sensitivity analysis of the Markov model simulation (Dapagliflozin group vs. Control group 1).

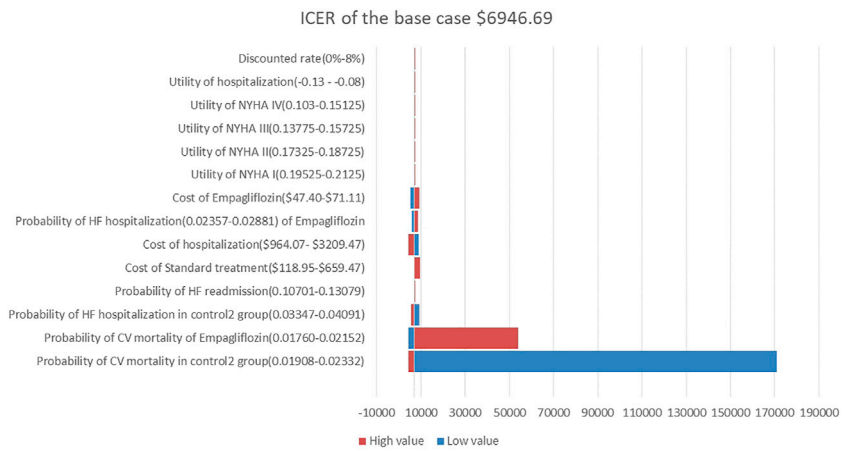

FIGURE 3 | Tornado diagram showing the univariate sensitivity analysis of the Markov model simulation. (Empagliflozin group vs. Control group 2).

medical cost of hospitalization for HF will save $1.4 billion, greatly reducing the burden on China's medical security system. There is a huge base of 8–10 million HF patients in China (The US Centers for Disease Control and Prevention, 2016), and up to half of them are HFrEF. Therefore, adding dapagliflozin to the standard treatment can reduce medical costs and improve the prognosis of HFrEF. Overall, our results provide decision-makers and healthcare payers with a valuable quantitative assessment of dapagliflozin.

In our one-way sensitivity analysis, it was found that CM in the dapagliflozin group and Control Group 1 had a great impact on the ICER, but the ICER was less than 1 fold per capita GDP, indicating that our model was stable and reliable. The CM in the empagliflozin group and Control Group 2 had a great impact on the ICER value, which was far more than 1 fold per capita GDP. We believe that this is due to the results of the EMPEROR-Reduced study that empagliflozin cannot reduce the risk of CM in patients with HFrEF (hazard ratio, 0.92; 95% CI, 0.75–1.12)

TABLE 4 | The result of scenario analyses presented as ICER.

Scenario	Dapagliflozin	Empagliflozin
	ICER(($ per QALY))	ICER(($per QALY))
Diabetes		
With	4,411.18	5,016.44
Without	6,790.06	10,844.36
Hospital characteristic		
Town Hospital	6,113.96	8,852.76
County Hospital	6,013.99	8,538.35
Municipal Hospital	5,589.93	7,204.65
Provincial Hospital	5,558.75	7,106.52
Ministerial Hospital	4,681.28	4,346.83
Time horizon		
5 years	8,493.52	9,975.67
10 years	5,589.93	7,204.65
15 years	4,600.59	5,359.84
20 years	4,151.68	5,077.71

(Mcmurray et al., 2019). If the range of this parameter is changed, the ICER will change significantly, which cannot be considered as the result of model instability. Whether adding dapagliflozin or empagliflozin to the standard treatment is cost-effective is mainly dependent on the clinical effects on the HFrEF patients, including reducing the risk of CM and the risk of hospitalization for HF.

In the PSA, it was found that the probability of adding dapagliflozin or empagliflozin was lower than that in other similar studies on HF (Savira et al., 2021; Van der Pol et al., 2017), whose probability was often more than 90%. This is because the medical system and economic status of these countries were different from those of China. The cost of hospitalization was $10,000, and the WTP ranged from $30,000 to $50,000. The scenario analysis also proved that the higher the cost of hospitalization, the more cost-effective it was.

Diabetes is closely related to HF, and it is estimated that 10% of diabetic patients suffer from HF (Bank et al., 2017). In fact, HF is the second most common CV manifestation of diabetes, and the prognosis of HF in diabetic patients is worse than that in non-diabetic patients (Bank et al., 2017; Shah et al., 2015; Jia et al., 2018). The DAPA-HF subgroup analysis showed that dapagliflozin reduces the risk of CV deaths by 15 and 21% in non-diabetic and diabetic populations, respectively (Petrie et al., 2020). Furthermore, dapagliflozin significantly reduced in people of varied ages (<55 years old, 55–64 years old, 65–74 years old, ≥ 75 years old) the risk of a CV death or an HF worsening by 13, 29, 24, and 32%, respectively (Martinez et al., 2020). In the scenario analysis, we also found that the ICER of the diabetic population was lower, and the longer the time of adding dapagliflozin to the standard treatment, the more cost-effective it was. Moreover, in China, compared with metformin and glimepiride, dapagliflozin was cost-effective in treating T2DM (Cai et al, 2019; Gu et al., 2016; Shao et al., 2017). Also, for patients with HFrEF and T2DM in China, adding dapagliflozin to their standard treatment not only greatly reduces the cost of medication and hospitalization, but is also more cost-effective.

In addition, the DAPA-HF study found that dapagliflozin could reduce the risk of CV death and hospitalization for HF in patients with HFrEF by 18 and 30%, respectively (Mcmurray et al., 2019), while the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study showed that compared with enalapril, SAC/VAL could reduce the risk of CV deaths and hospitalization for HF in patients with HFrEF by 20 and 21%, respectively (Mcmurray et al., 2014). Although there is no prospective study comparing the effects of dapagliflozin and SAC/VAL in the treatment of HFrEF, the results of clinical trials are similar. According to the latest national negotiation price in 2020, SAC/VAL is $3.5 per 200 mg twice daily, the daily

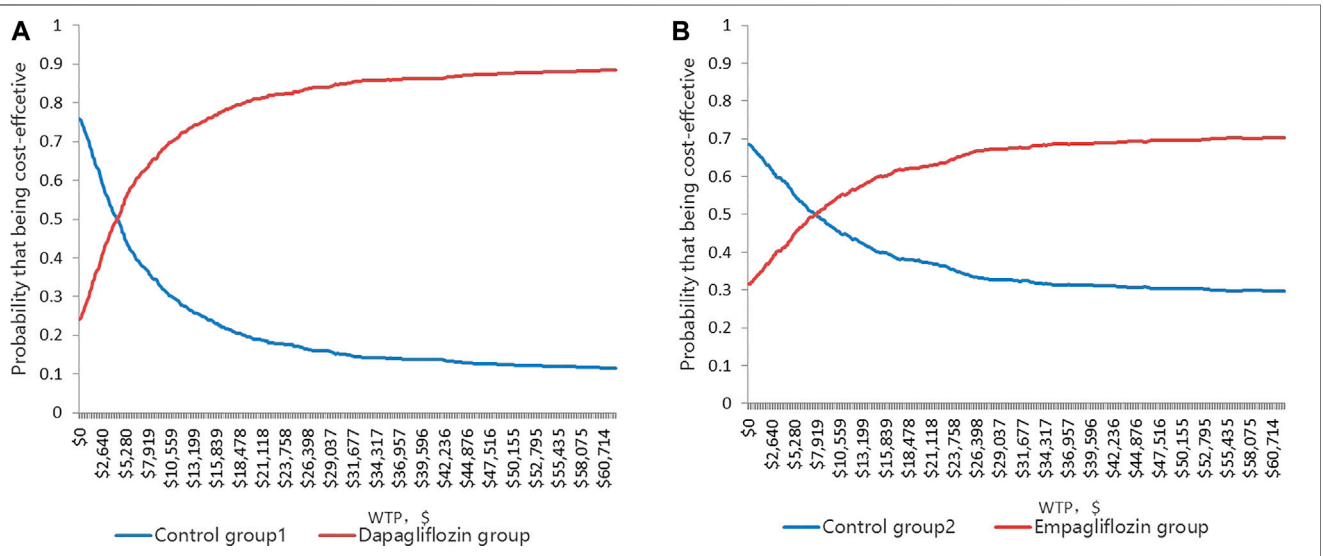

FIGURE 4 | (A) Cost-effectiveness acceptability curve showing the maximum willingness to pay and the corresponding probability of cost-effectiveness for Dapagliflozin group and Control group 1. **(B)** Cost-effectiveness acceptability curve showing the maximum willingness to pay and the corresponding probability of cost-effectiveness for Empagliflozin group and Control group 2.

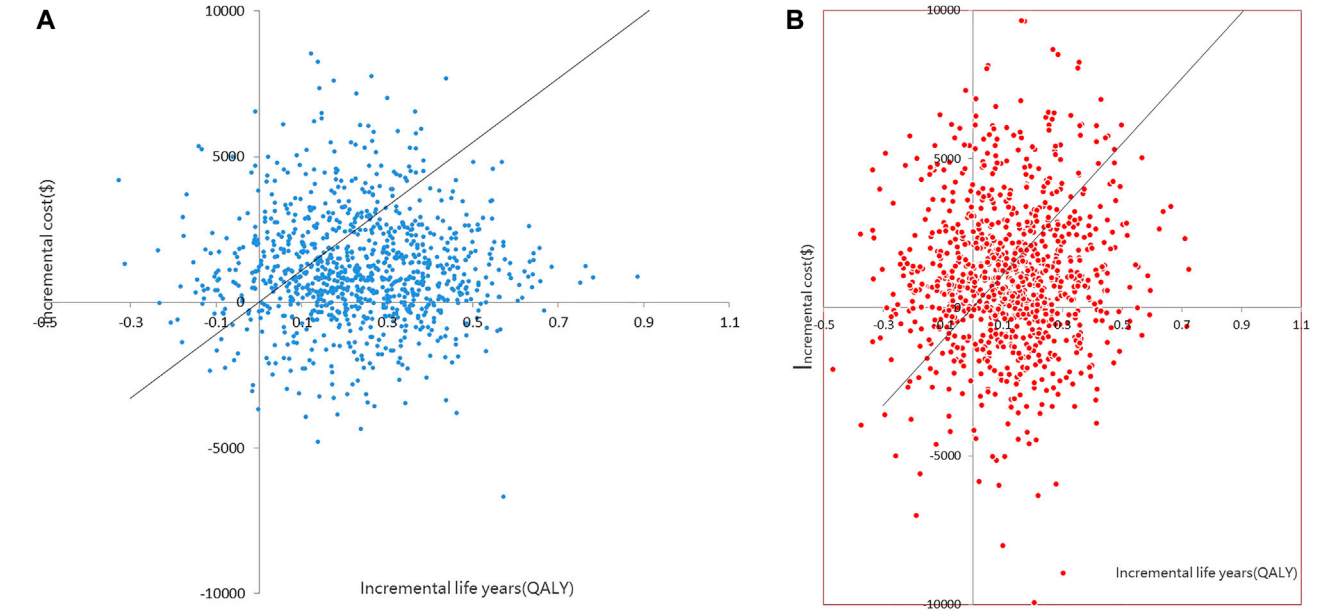

FIGURE 5 | (A) Scatter plot showing the incremental costs and incremental quality-adjusted life-year of a thousand simulations for Dapagliflozin group and Control group 1. **(B)** Scatter plot showing the incremental costs and incremental quality-adjusted life-year of a thousand simulations for Empagliflozin group and Control group 2).

cost is about $6.18 in the PARADIGM-HF study; dapagliflozin is $0.677 per 10 mg daily, the daily cost is about $0.677 for low-income patients; and dapagliflozin is the first-choice drug.

There were some limitations in this study. First, our model did not consider hospitalization for non-HF, but in the DAPA-HF and EMPEROR-Reduced studies, the hazard ratio of all-cause hospitalization was 0.75 and 0.85, respectively (Mcmurray et al., 2019; Packer et al., 2020), and our results could be conservative. Second, we could not obtain data regarding dapagliflozin and empagliflozin in patients with HFrEF in China and the health utility of each state, which may lead to some racial bias in the simulation results. Third, we assumed that HF patients in China could tolerate the recommended dose of each drug, regardless of the adverse events. In the DAPA-HF and EMPEROR-Reduced studies, the most common adverse events including hypovolemia, renal failure, amputation, diabetic ketoacidosis, and gangrene were not significantly different. Fourth, other possible real-world treatment strategies were not calculated, such as drug switching, drug compliance heart transplantation, etc. Finally, in our model, the transition probability is fixed, which is not calculated by age distribution, but as the age becomes older, the clinical benefit of dapagliflozin is higher (Martinez et al., 2020), and the ICER is smaller, which further emphasizes that the results of the analysis may be conservative.

CONCLUSION

In conclusion, our analysis provided an insight into the cost-effectiveness of adding dapagliflozin or empagliflozin in treating HFrEF patients compared with only the standard treatment. Adding dapagliflozin was considered cost-effective based on the perspective of the Chinese public healthcare system. Accordingly, our findings will help healthcare providers make decisions. Additional real-world studies on the cost-effectiveness of dapagliflozin or empagliflozin based on the Chinese population need to be conducted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RZ collected the data regarding heart failure; YJ analyzed the data and developed a Markov model; HS was the leader of the study. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.733681/full#supplementary-material

REFERENCES

Andreadou, I., Bell, R. M., Bøtker, H. E., and Zuurbier, C. J. (2020). SGLT2 Inhibitors Reduce Infarct Size in Reperfused Ischemic Heart and Improve Cardiac Function during Ischemic Episodes in Preclinical Models. *Biochim. Biophys. Acta Mol. Basis Dis.* 1866 (7), 165770. doi:10.1016/j.bbadis.2020.165770

Anker, S. D., Butler, J., Filippatos, G., Khan, M. S., Marx, N., Lam, C. S. P., et al. (2021b). Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients with Heart Failure by Baseline Diabetes Status: Results from the EMPEROR-Reduced Trial. *Circulation* 143 (4), 337–349. doi:10.1161/CIRCULATIONAHA.120.051824

Anker, S. D., Butler, J., Filippatos, G., Ferreira, J. P., Bocchi, E., Bohm, M., et al. (2021a). Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N. Engl. J. Med.* 385 (16), 1451–1461. doi:10.1056/NEJMoa2107038

Bank, I. E. M., Gijsberts, C. M., Teng, T. K., Benson, L., Sim, D., Yeo, P. S. D., et al. (2017). Prevalence and Clinical Significance of Diabetes in Asian versus White Patients with Heart Failure. *JACC Heart Fail.* 5 (1), 14–24. doi:10.1016/j.jchf.2016.09.015

Cai, X., Shi, L., Yang, W., Gu, S., Chen, Y., Nie, L., et al. (2019). Cost-effectiveness Analysis of Dapagliflozin Treatment versus Metformin Treatment in Chinese Population with Type 2 Diabetes. *J. Med. Econ.* 22 (4), 336–343. doi:10.1080/13696998.2019.1570220

Chao, E. C., and Henry, R. R. (2010). SGLT2 Inhibition-Aa Novel Strategy for Diabetes Treatment. *Nat. Rev. Drug Discov.* 9 (7), 551–559. doi:10.1038/nrd3180

Conrad, N., Judge, A., Tran, J., Mohseni, H., Hedgecott, D., Crespillo, A. P., et al. (2018). Temporal Trends and Patterns in Heart Failure Incidence: a Population-Based Study of 4 Million Individuals. *Lancet* 391 (10120), 572–580. doi:10.1016/S0140-6736(17)32520-5

Cook, C., Cole, G., Asaria, P., Jabbour, R., and Francis, D. P. (2014). The Annual Global Economic burden of Heart Failure. *Int. J. Cardiol.* 171 (3), 368–376. doi:10.1016/j.ijcard.2013.12.028

Desai, A. S., and Stevenson, L. W. (2012). Rehospitalization for Heart Failure: Predict or Prevent? *Circulation* 126 (4), 501–506. doi:10.1161/CIRCULATIONAHA.112.125435

Eichler, H. G., Kong, S. X., Gerth, W. C., Mavros, P., and Jönsson, B. (2004). Use of Cost-Effectiveness Analysis in Health-Care Resource Allocation Decision-Making: How Are Cost-Effectiveness Thresholds Expected to Emerge? *Value Health* 7 (5), 518–528. doi:10.1111/j.1524-4733.2004.75003.x

Garcia-Ropero, A., Santos-Gallego, C. G., Zafar, M. U., and Badimon, J. J. (2019). Metabolism of the Failing Heart and the Impact of SGLT2 Inhibitors. *Expert Opin. Drug Metab. Toxicol.* 15 (4), 275–285. doi:10.1080/17425255.2019.1588886

Greene, S. J., Fonarow, G. C., Vaduganathan, M., Khan, S. S., Butler, J., and Gheorghiade, M. (2015). The Vulnerable Phase after Hospitalization for Heart Failure. *Nat. Rev. Cardiol.* 12 (4), 220–229. doi:10.1038/nrcardio.2015.14

Gu, D., Huang, G., He, J., Wang, X., and Duan, x. (2003). Investigation of Prevalence and Distributing Feature of Chronic Heart Failure in China Adult Popuation. *Chin. J. Cardio* 1 (31), 3–6. doi:10.3760/j:issn:0253-3758.2003.01.002

Gu, S., Mu, Y., Zhai, S., Zeng, Y., Zhen, X., and Dong, H. (2016). Cost-Effectiveness of Dapagliflozin versus Acarbose as a Monotherapy in Type 2 Diabetes in China. *PLoS One* 11 (11), e0165629. doi:10.1371/journal.pone.0165629

Huang, J., Yin, H., Zhang, M., Ni, Q., and Xuan, J. (2017). Understanding the Economic burden of Heart Failure in China: Impact on Disease Management and Resource Utilization. *J. Med. Econ.* 20 (5), 549–553. doi:10.1080/13696998.2017.1297309

Iorga, R. A., Bacalbasa, N., Carsote, M., Bratu, O. G., Stanescu, A. M. A., Bungau, S., et al. (2020). Metabolic and Cardiovascular Benefits of GLP-1 Agonists, besides the Hypoglycemic Effect (Review). *Exp. Ther. Med.* 20 (3), 2396–2400. doi:10.3892/etm.2020.8714

Jensen, J., Omar, M., Kistorp, C., Poulsen, M. K., Tuxen, C., Gustafsson, I., et al. (2020). Twelve Weeks of Treatment with Empagliflozin in Patients with Heart Failure and Reduced Ejection Fraction: A Double-Blinded, Randomized, and Placebo-Controlled Trial. *Am. Heart J.* 228, 47–56. doi:10.1016/j.ahj.2020.07.011

Jia, G., Whaley-Connell, A., and Sowers, J. R. (2018). Diabetic Cardiomyopathy: a Hyperglycaemia- and Insulin-Resistance-Induced Heart Disease. *Diabetologia* 61 (1), 21–28. doi:10.1007/s00125-017-4390-4

King, J. B., Shah, R. U., Bress, A. P., Nelson, R. E., and Bellows, B. K. (2016). Cost-Effectiveness of Sacubitril-Valsartan Combination Therapy Compared with Enalapril for the Treatment of Heart Failure with Reduced Ejection Fraction. *JACC Heart Fail.* 4 (5), 392–402. doi:10.1016/j.jchf.2016.02.007

Krittayaphong, R., and Permsuwan, U. (2021). Cost-utility Analysis of Add-On Dapagliflozin Treatment in Heart Failure with Reduced Ejection Fraction. *Int. J. Cardiol.* 322, 183–190. doi:10.1016/j.ijcard.2020.08.017

Lymperopoulos, A., Borges, J. I., Cora, N., and Sizova, A. (2021). Sympatholytic Mechanisms for the Beneficial Cardiovascular Effects of SGLT2 Inhibitors: A Research Hypothesis for Dapagliflozin's Effects in the Adrenal Gland. *Ijms* 22 (14), 7684. doi:10.3390/ijms22147684

Ma, X. W. (2020). *China Health Statistics Yearbook 2020*. Beijing: China Union Medical University Press.

Martinez, F. A., Serenelli, M., Nicolau, J. C., Petrie, M. C., Chiang, C. E., Tereshchenko, S., et al. (2020). Efficacy and Safety of Dapagliflozin in Heart Failure with Reduced Ejection Fraction According to Age: Insights from DAPA-HF. *Circulation* 141 (2), 100–111. doi:10.1161/CIRCULATIONAHA.119.044133

Mcewan, P., Darlington, O., Mcmurray, J. J. V., Jhund, P. S., Docherty, K. F., Böhm, M., et al. (2020). Cost-effectiveness of Dapagliflozin as a Treatment for Heart Failure with Reduced Ejection Fraction: a Multinational Health-Economic Analysis of DAPA-HF. *Eur. J. Heart Fail.* 22 (11), 2147–2156. doi:10.1002/ejhf.1978

Mcmurray, J. J., Packer, M., Desai, A. S., Gong, J., Lefkowitz, M. P., Rizkala, A. R., et al. (2014). Angiotensin-neprilysin Inhibition versus Enalapril in Heart Failure. *N. Engl. J. Med.* 371 (11), 993–1004. doi:10.1056/NEJMoa1409077

Mcmurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., et al. (2019). Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* 381 (21), 1995–2008. doi:10.1056/NEJMoa1911303

Nassif, M. E., Qintar, M., Windsor, S. L., Jermyn, R., Shavelle, D. M., Tang, F., et al. (2021). Empagliflozin Effects on Pulmonary Artery Pressure in Patients with Heart Failure: Results from the EMBRACE-HF Trial. *Circulation* 143 (17), 1673–1686. doi:10.1161/CIRCULATIONAHA.120.052503

National Bureau of statistics of the people's Republic of China (2019). *China Health Statistics Yearbook 2019*. Beijing: Peking Union Medical College Press.

National Center for Chronic and Noncommunicable Disease Control and Prevention (2019).Chinese Center for Disease Control and Prevention, in *China Mortality Surveillance Dataset 2018* (Beijing: China Science and Technology Press).

Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., Carson, P., et al. (2020). Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* 383 (15), 1413–1424. doi:10.1056/NEJMoa2022190

Park, S. K., Hong, S. H., Kim, H., Kim, S., and Lee, E. K. (2019). Cost-Utility Analysis of Sacubitril/Valsartan Use Compared with Standard Care in Chronic Heart Failure Patients with Reduced Ejection Fraction in South Korea. *Clin. Ther.* 41 (6), 1066–1079. doi:10.1016/j.clinthera.2019.04.031

Petrie, M. C., Verma, S., Docherty, K. F., Inzucchi, S. E., Anand, I., Belohlávek, J., et al. (2020). Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients with Heart Failure with and without Diabetes. *JAMA* 323 (14), 1353–1368. doi:10.1001/jama.2020.1906

Requena-Ibáñez, J. A., Santos-Gallego, C. G., Rodriguez-Cordero, A., Vargas-Delgado, A. P., Mancini, D., Sartori, S., et al. (2021). Mechanistic Insights of Empagliflozin in Nondiabetic Patients with HFrEF: From the EMPA-TROPISM Study. *JACC Heart Fail.* 9 (8), 578–589. doi:10.1016/j.jchf.2021.04.014

Research group of China Pharmacoeconomics Evaluation (2019). ChinaGuidelinesforPharmacoeconomicEvaluations. *China Pharmacoeconomics (Chinese)* 7 (3), 11–48. 6-9.

Santos-Gallego, C. G., Requena-Ibanez, J. A., San Antonio, R., Garcia-Ropero, A., Ishikawa, K., Watanabe, S., et al. (2021). Empagliflozin Ameliorates Diastolic Dysfunction and Left Ventricular Fibrosis/Stiffness in Nondiabetic Heart Failure: A Multimodality Study. *JACC Cardiovasc. Imaging* 14 (2), 393–407. doi:10.1016/j.jcmg.2020.07.042

Savira, F., Wang, B. H., Kompa, A. R., Ademi, Z., Owen, A. J., Zoungas, S., et al. (2021). Cost-effectiveness of Dapagliflozin in Chronic Heart Failure: an Analysis from the Australian Healthcare Perspective. *Eur. J. Prev. Cardiol.* 28 (9), 975–982. doi:10.1177/2047487320938272

Shah, A. D., Langenberg, C., Rapsomaniki, E., Denaxas, S., Pujades-Rodriguez, M., Gale, C. P., et al. (2015). Type 2 Diabetes and Incidence of Cardiovascular Diseases: a Cohort Study in 1·9 Million People. *Lancet Diabetes Endocrinol.* 3 (2), 105–113. doi:10.1016/S2213-8587(14)70219-0

Shao, H., Zhai, S., Zou, D., Mir, M. U., Zawadzki, N. K., Shi, Q., et al. (2017). Cost-effectiveness Analysis of Dapagliflozin versus Glimepiride as Monotherapy in a Chinese Population with Type 2 Diabetes Mellitus. *Curr. Med. Res. Opin.* 33 (2), 359–369. doi:10.1080/03007995.2016.1257978

The People's Bank of China (2020). *Foreign Exchange Rates* Beijing, China: Peking Union Medical College Press.

The US Centers for Disease Control and Prevention (2016). *CDC in China: factsheet*. Atlanta, USA: Centers for Disease Controland Prevention. Avaiable at: http://www.cdc.gov/globalhealth/countries/china/pdf/china.pdf (Accessed July 21, 2016).

Van der Pol, S., Degener, F., Postma, M. J., and Vemer, P. (2017). An Economic Evaluation of Sacubitril/Valsartan for Heart Failure Patients in the Netherlands. *Value Health* 20 (3), 388–396. doi:10.1016/j.jval.2016.10.015

Virani, S. S., Alonso, A., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., et al. (2020). Heart Disease and Stroke Statistics-2020 Update: A Report from the American Heart Association. *Circulation* 141 (9), e139–e596. doi:10.1161/CIR.0000000000000757

Wu, Y., Tian, S., Rong, P., Zhang, F., Chen, Y., Guo, X., et al. (2020). Sacubitril-Valsartan Compared with Enalapril for the Treatment of Heart Failure: A Decision-Analytic Markov Model Simulation in China. *Front. Pharmacol.* 11, 1101. doi:10.3389/fphar.2020.01101

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SYSTEMATIC REVIEW
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Comparison of Five Prophylactically Intravenous Drugs in Preventing Opioid-Induced Cough: A Bayesian Network Meta-Analysis of Randomized Controlled Trials

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Background: Due to the absence of direct comparisons of different therapeutic drugs in preventing opioid-induced cough (OIC) during the induction of general anesthesia, clinicians often faced difficulties in choosing the optimal drug for these patients. Hence, this network meta-analysis was conducted to solve this problem.

Methods: Online databases, including Pubmed, Embase, Web of Science, Cochrane, and Google Scholar, were searched comprehensively to identify eligible randomized controlled trials (RCTs), up to March 15th, 2021. Within a Bayesian framework, network meta-analysis was performed by the "gemtc" version 0.8.2 package of R-3.4.0 software, and a pooled risk ratio (RR) associated with 95% credible interval (CrI) was calculated.

Results: A total of 20 RCTs were finally enrolled, and the overall heterogeneity for this study was low to moderate. Traditional pair-wise meta-analysis results indicated that all of the five drugs, namely, lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine could prevent OIC for four clinical outcomes, compared with the placebo (all *p-values* < 0.05). Moreover, dezocine had the best effect, compared with that of the other drugs (all *p-values* < 0.05). Network meta-analysis results suggested that the top three rank probabilities for four clinical outcomes from best to worst were dezocine, butorphanol, and ketamine based on individual/cumulative rank plots and surface under the cumulative ranking curve (SUCRA) probabilities. The node-splitting method indicated the consistency of the direct and indirect evidence.

Conclusions: Our results indicated that all of these five drugs could prevent OIC compared with the placebo. Moreover, the top three rank probabilities for four clinical outcomes from best to worst were dezocine, butorphanol, and ketamine. Our results were anticipated to provide references for guiding clinical research, and further high-quality RCTs were required to verify our findings.

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/], identifier [CRD42021243358].

Keywords: drugs, pharmacological interventions, network meta-analysis, opioid-induced cough, randomized controlled trials

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INTRODUCTION

Due to the rapid onset, short duration, strong analgesia, and reduced cardiovascular response, opioids such as sufentanil, fentanyl, and remifentanil have been widely applied in the induction and maintenance of general anesthesia (Liu et al., 2014; Shuying et al., 2016). However, the complication of opioid-induced cough (OIC) is frequently encountered during the induction of anesthesia, with an incidence rate as high as 65% (Sun et al., 2014). Although most OIC is transient, light, and self-limiting, it is a risk factor for postoperative nausea and vomiting (Peringathara and Robinson, 2016) and is extremely dangerous for patients with comorbidities, such as brain hernia, increased intracranial pressure, increased ocular pressure, open eye injury, pneumothorax, and hypersensitive airway disease (Lin et al., 2005; Yu et al., 2007). Hence, there is an urgent need to take measures to prevent the occurrence of OIC during induction of general anesthesia.

Numerous pharmacological or non-pharmacological measures have been taken to prevent OIC. Therein, non-pharmacological measures are characterized by diluting drug concentration, slowing down injection rate, using the peripheral injection site, reducing the drug dose, instructing patients on performing the huffing maneuver, and verifying the proper administration sequence of the drug (Ambesh et al., 2010; Min et al., 2012; Shrestha et al., 2012; Xiong et al., 2020). Currently, pharmacological interventions have been widely used in the clinical setting, including lidocaine, dezocine, dexmedetomidine, ketamine, and butorphanol (Shuying et al., 2016; Zhang et al., 2018; Clivio et al., 2019). However, most of these articles were compared with the placebo, and direct comparisons of different pharmacological interventions were absent, along with the application of novel drugs. As a result, it was much harder for clinical physicians to choose the optimal therapeutic drug.

As is already known, network meta-analysis could overcome the limitations of traditional meta-analysis and gain evidence directly and indirectly (Lumley, 2002; Zhang et al., 2019). Hence, we applied a Bayesian network meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of different pharmacological interventions for OIC. In this article, five different therapeutic drugs, namely, lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine were finally enrolled. Four clinical outcomes comprising incidence of OIC, mild severity of OIC, moderate severity of OIC, and severe severity of OIC were ultimately evaluated. Our results were anticipated to provide some references for guiding clinical practice.

MATERIALS AND METHODS

Search Strategy

This network meta-analysis was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). Online databases, including Pubmed, Embase, Web of Science, Cochrane, and Google Scholar, were searched comprehensively to identify eligible randomized controlled trials (RCTs) up to March 15th, 2021. Our search strategy was mainly comprised three parts utilizing the following keywords in combination with the following Medical Subject Heading (MeSH) terms and text words: "therapeutic drugs", "lidocaine", "ketamine", "dezocine", "butorphanol", or "dexmedetomidine" and "opioid-induced cough", "sufentanil-induced cough", "fentanyl-induced cough", or "remifentanil-induced cough" and ("randomized controlled trials"). Additional articles were manually screened from the reference lists of eligible studies to avoid omissions. This network meta-analysis was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) with the registration number "CRD42021243358".

Inclusion and Exclusion Criteria

The inclusion criteria in this article were displayed as following: 1) English articles; 2) Randomized controlled trials; 3) At least two of six drugs (lidocaine, ketamine, dezocine, butorphanol, dexmedetomidine, and placebo) should be compared; 4) At least one of four clinical outcomes (incidence of OIC, mild severity of OIC, moderate severity of OIC, and severe severity of OIC) should be evaluated; and 5) Data could be extracted from articles; The exclusion criteria were detailed as follows: 1)Non-English articles; 2) Non-randomized controlled trials; 3) Articles that did not compare at least two of these six drugs; 4) Articles that did not evaluate at least one of four clinical outcomes; and 5) Data could not be extracted from articles;

Data Extraction

Two blind reviewers independently identified the data of eligible studies, based on our inclusion and exclusion criteria. When any discrepancy existed, we would discuss with a third reviewer to solve this problem. Moreover, we would record the following information for further analysis: the first author's name of the study, publication year, American Society of Anesthesiologist (ASA) physical status, injection, study type, opioid, treatment, incidence of OIC, mild severity of OIC, moderate severity of OIC, and severe severity of OIC.

Quality Assessment

In this article, the potential source of bias of eligible RCTs would be evaluated based on the Cochrane Handbook (http://www.cochrane-handbook.org) (Higgins et al., 2019), containing the following seven aspects of bias: 1) Random sequence generation (selection bias); 2) Allocation concealment (selection bias); 3) Blinding of participants and personnel (performance bias); 4) Blinding of outcome assessment (detection bias); 5) Incomplete outcome data (attrition bias); 6) Selective reporting (reporting bias); and 7) Other bias. Finally, each aspect would be graded as a low, high, or unclear risk of bias.

Statistical Analysis

Within a Bayesian framework, network meta-analysis comprising different therapeutic drugs was performed by the version 0.8.2 "gemtc" package of R software (version 3.4.0; R

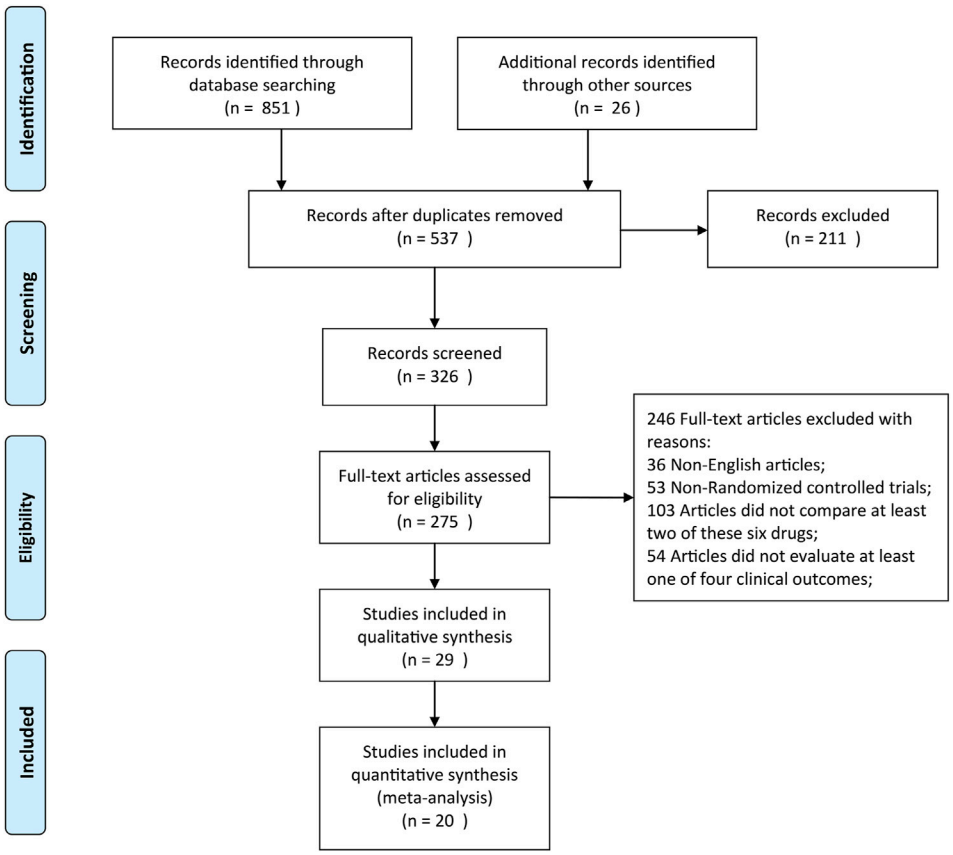

FIGURE 1 | Flow diagram of the literature selection process.

Foundation, Vienna, Austria) (Lumley, 2002; Valkenhoef and Kuiper, 2016). A non-informative prior distribution was utilized in this Bayesian analysis, and posterior distribution was estimated by Gibbs sampling using the Markov chain Monte Carlo method (Ando et al., 2020; Cha et al., 2021). When three Markov chains run simultaneously, 10,000 simulations and 40,000 iterations were set by us for each chain to calculate the risk ratio (RR) with 95% credible interval (CrI) of model parameters by the mtc.run function. The Brooks–Gelman–Rubin plot, trace plot, and density plot mehods were utilized to assess the model convergence (Wu et al., 2013). Moreover, we would simultaneously obtain the matrix and the plot of rank probabilities, provided by the R package of "gemtc". When a loop connecting three arms existed, the node-splitting method was utilized to access the inconsistency by reporting its Bayesian *p*-value (Dias et al., 2010; Wang et al., 2018). To evaluate the heterogeneity, the mtc. anohe command of the R package of "gemtc" was utilized by reporting the heterogeneity variance parameter I^2. $I^2 > 50\%$ was regarded as significant heterogeneity, and the random effects models would be utilized; otherwise the fixed effect models would be utilized (Ma et al., 2021; Zhou et al., 2021). Sensitivity analysis was also conducted to examine the robustness of our results. In summary, all *p*-values were adopted by a two-sided test, and $p\text{-value} < 0.05$ was considered to be statistically significant.

RESULTS

Search Results and Study Characteristics

A total of 877 citations were yielded by searching five online databases (Pubmed, Embase, Web of Science, Cochrane, and Google Scholar) by our search strategy. Based on the inclusion and exclusion criteria, 20 RCTs were finally identified and considered eligible for this network meta-analysis (**Figure 1**) (Lin et al., 2004; Pandey et al., 2004; Pandey et al., 2005; Yeh et al., 2007; Kim et al., 2008; Kim et al., 2009; Bang et al., 2010; Guler et al., 2010; Sun et al., 2011; He et al., 2012; Yu et al., 2012; Gecaj-Gashi et al., 2013; Honarmand et al., 2013; Sun and Huang, 2013; Saleh et al., 2014; Liu et al., 2015; Cheng et al., 2016; Naldan et al., 2019; Yin and Zhang, 2019; Zhou et al., 2019). Moreover, **Table 1** summarizes the detailed information of individual studies enrolled in this network meta-analysis. As for quality assessment, all of the 20 RCTs were evaluated based on the Cochrane Handbook (http://www.cochrane-handbook.org) and graded each potential source of bias as low, high, or unclear risk of bias (Supplement **Supplementary Figures S1, S2**). Moreover, the

TABLE 1 | Detailed information of individual studies enrolled in this network meta-analysis.

Study	Year	ASA	Injection	Study type	Opioid	Treatment	Incidence of OIC		Mild severity of OIC		Moderate severity of OIC		Severe severity of OIC	
							Responders	Sample size	Responders	Sample size	Responders	sampleSize	Responders	sampleSize
Yin	2019	I-II	Intravenous	RCT	sufentanil	placebo	33	40	5	40	16	40	12	40
						butorphanol	0	80	0	80	0	80	0	80
Zhou	2019	I-II	Intravenous	RCT	fentanyl	placebo	22	42	8	42	8	42	6	42
						dexmedetomidine	29	126	16	126	8	126	5	126
Naldan	2019	I	Intravenous	RCT	fentanyl	placebo	16	40	7	40	6	40	2	40
						lidocaine	6	40	4	40	2	40	0	40
Cheng	2016	I-II	Intravenous	RCT	fentanyl	placebo	33	105	20	105	7	105	6	105
						butorphanol	16	210	15	210	1	210	0	210
Liu	2015	I-II	Intravenous	RCT	sufentanil	placebo	59	185	13	185	21	185	25	185
						dezocine	0	185	0	185	0	185	0	185
Saleh	2014	I-II	Intravenous	RCT	fentanyl	placebo	53	100	25	100	17	100	11	100
						ketamine	20	100	10	100	6	100	4	100
						dexmedetomidine	34	100	16	100	11	100	7	100
Gecaj-Gashi	2013	I-II	Intravenous	RCT	fentanyl	placebo	27	62	19	62	5	62	3	62
						lidocaine	24	124	18	124	5	124	1	124
Honarmand	2013	I-II	Intravenous	RCT	remifentanil	placebo	17	30	8	30	8	30	1	30
						ketamine	6	30	4	30	2	30	0	30
Sun	2013	I-II	Intravenous	RCT	sufentanil	placebo	16	60	6	60	5	60	5	60
						dexmedetomidine	11	180	4	180	3	180	4	180
He	2012	I-II	Intravenous	RCT	fentanyl	placebo	61	100	30	100	23	100	8	100
						dexmedetomidine	58	200	29	200	22	200	7	200
Yu	2012	I-II	Intravenous	RCT	fentanyl	placebo	45	110	21	110	13	110	11	110
						dexmedetomidine	25	110	10	110	7	110	8	110
Sun	2011	I-II	Intravenous	RCT	fentanyl	placebo	42	60	NA	NA	NA	NA	NA	NA
						dezocine	0	60	NA	NA	NA	NA	NA	NA
Guler	2010	I-II	Intravenous	RCT	fentanyl	placebo	23	100	10	100	12	100	1	100
						lidocaine	11	100	7	100	4	100	0	100
						ketamine	0	100	0	100	0	100	0	100
Bang	2010	I-II	Intravenous	RCT	remifentanil	placebo	24	79	17	79	5	79	2	79
						lidocaine	20	79	7	79	6	79	7	79
Kim	2009	I-II	Intravenous	RCT	remifentanil	placebo	43	154	23	154	12	154	8	154
						ketamine	18	156	10	156	4	156	4	156
Kim	2008	I-II	Intravenous	RCT	remifentanil	placebo	69	250	33	250	21	250	15	250
						lidocaine	38	250	22	250	10	250	6	250
Yeh	2007	I-II	Intravenous	RCT	fentanyl	placebo	39	180	26	180	9	180	4	180
						ketamine	13	180	9	180	4	180	0	180
Pandey	2005	I-II	Intravenous	RCT	fentanyl	placebo	28	80	21	80	6	80	1	80
						lidocaine	34	240	22	240	11	240	1	240
Lin	2004	I-II	Intravenous	RCT	fentanyl	placebo	20	31	NA	NA	NA	NA	NA	NA
						lidocaine	4	29	NA	NA	NA	NA	NA	NA
Pandey	2004	I-II	Intravenous	RCT	fentanyl	placebo	86	251	60	251	21	251	5	251
						lidocaine	33	251	23	251	7	251	3	251

OIC: opioid-induced cough; ASA: American Society of Anesthesiologist physical status; RCT: randomized controlled trials; NA: not available.

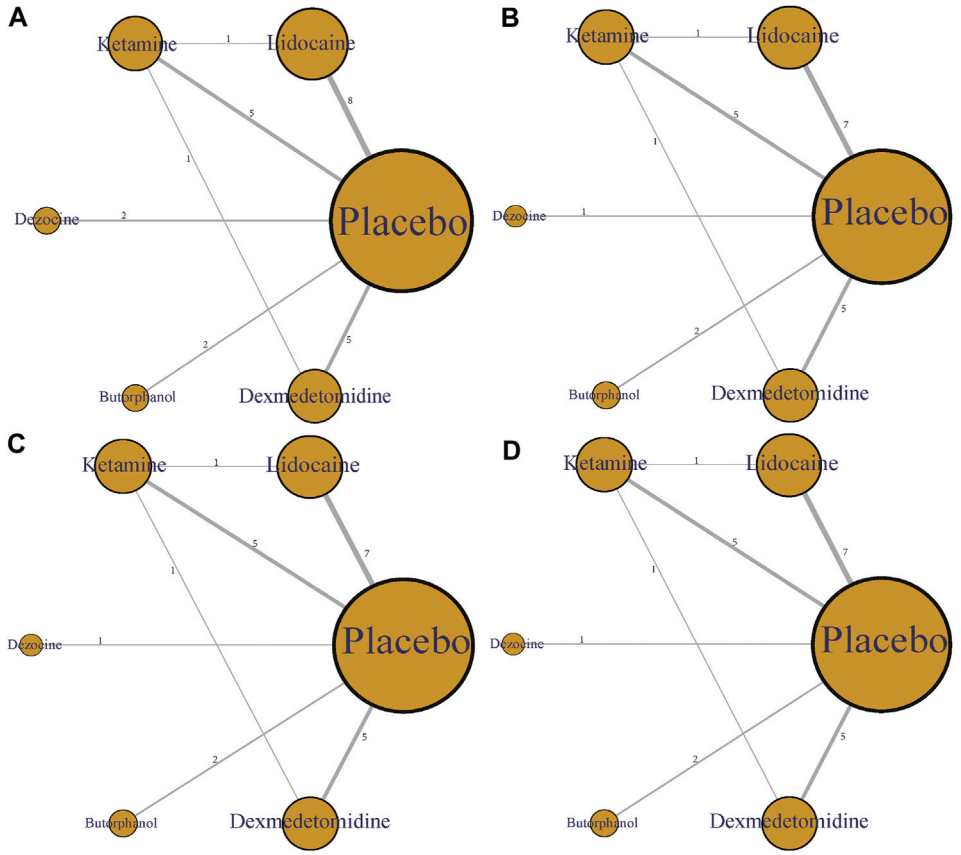

FIGURE 2 | Network structure diagrams. **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC. The numbers showed the number of direct comparisons. Line thicknesses were proportional to the number of direct comparisons. Circle diameters were proportional to the treatment numbers.

PRISMA 2020 checklist and PRISMA 2020 for abstract checklist are displayed in **Supplementary Tables S1, S2**, respectively.

Network Structure Diagrams

In this article, five different therapeutic drugs, namely, lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine were finally enrolled. Four clinical outcomes comprising incidence of OIC, mild severity of OIC, moderate severity of OIC, and severe severity of OIC were ultimately evaluated. As displayed in **Figure 2**, the network structure diagrams detailed the direct comparisons between different drugs in the four clinical outcomes, respectively. Besides, the numbers showed the number of direct comparisons. Line thicknesses were proportional to the number of direct comparisons. Circle diameters were proportional to the treatment numbers included in this network meta-analysis.

Incidence of OIC

A total of 20 RCTs, including six drugs (lidocaine, ketamine, dezocine, butorphanol, dexmedetomidine, and placebo) contributed to the clinical outcome of the incidence of OIC. As displayed in **Figure 3A** and **Supplementary Figure S3A**, it detailed the efficacy of different comparisons of drugs by RRs and corresponding 95% CrIs. We could easily find that all of the five drugs (lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine) could prevent the incidence of OIC, compared with the placebo (all *p-values* < 0.05). Moreover, dezocine had the best effect, compared with that of the other drugs (all-values $p < 0.05$). **Figure 4A** summarizes the heterogeneity between different comparisons of drugs. Individual and cumulative rank plots indicated that the rank probability for the incidence of OIC from best to worst was dezocine, butorphanol, ketamine, dexmedetomidine, lidocaine, and placebo (**Figure 5A**, **Figure 6A**). Moreover, their surface under the cumulative ranking curve (SUCRA) probabilities of six drugs for the incidence of OIC are also presented in **Figure 7A**; **Table 2**. Additionally, *p*- values of the node-splitting method between ketamine vs lidocaine were below 0.05, indicating the inconsistency of the direct and indirect evidence. *P-values* values of the node-splitting method between dexmedetomidine vs. ketamine were above 0.05, suggesting the consistency of the direct and indirect evidence (**Figure 8A**). Sensitivity analysis was also conducted as shown in **Supplementary Figure S4A**, indicating the robustness of our results.

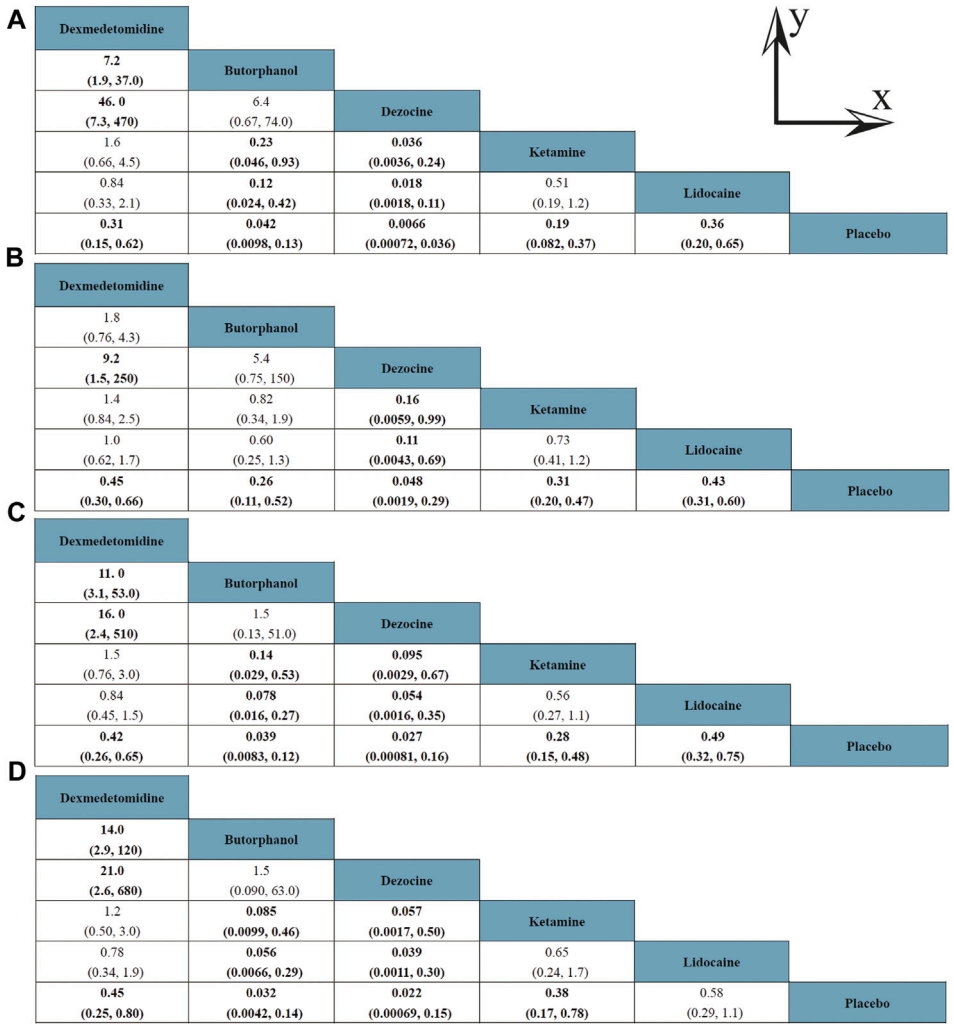

FIGURE 3 | Efficacy of different comparisons of drugs by RRs and corresponding 95% CrIs; **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC. All results were displayed as the ratio of the *Y* axis versus *X* axis. Bold fonts indicated *p-value* < 0.05.

Mild Severity of OIC

18 RCTs contributed to the analysis of mild severity of OIC, including six drugs, namely, lidocaine, ketamine, dezocine, butorphanol, dexmedetomidine, and placebo. **Figure 3B**; **Supplementary Figure S3B** details the efficacy of different comparisons of drugs by RRs and corresponding 95% CrIs. Similar to previous results, all of the five drugs (lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine) could reduce mild severity of OIC, compared with that of the placebo (all *p-values* < 0.05). Moreover, dezocine had the best effect compared with that of other drugs (all *p-values* < 0.05). Heterogeneity between different comparisons of drugs is summarized in **Figure 4B**. Individual and cumulative rank plots explained that the rank probability for mild severity of OIC from first to last was dezocine, butorphanol, ketamine, lidocaine, dexmedetomidine, and placebo (**Figure 5B**, **Figure 6B**). Moreover, their surface under the cumulative ranking curve (SUCRA) probabilities of the six drugs for mild severity of OIC are also shown in **Figure 7B**; **Table 2**. Besides, *p*-values of the node-splitting method between ketamine vs. lidocaine were below 0.05, indicating the inconsistency of the direct and indirect evidence. *P*-values of the node-splitting method between dexmedetomidine vs. ketamine were more than 0.05, suggesting the consistency of the direct and indirect evidence (**Figure 8B**). Sensitivity analysis was also conducted as shown in **Supplementary Figure S4B**, indicating the robustness of our results.

Moderate Severity of OIC

There were 18 RCTs contributing to the analysis of moderate severity of OIC, including six drugs (lidocaine, ketamine, dezocine, butorphanol, dexmedetomidine, and placebo). **Figure 3C**; **Supplementary Figure S3C** detailed the efficacy of different comparisons of drugs by RRs and corresponding 95% CrIs. As same as previous results, all of the five drugs (lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine) could

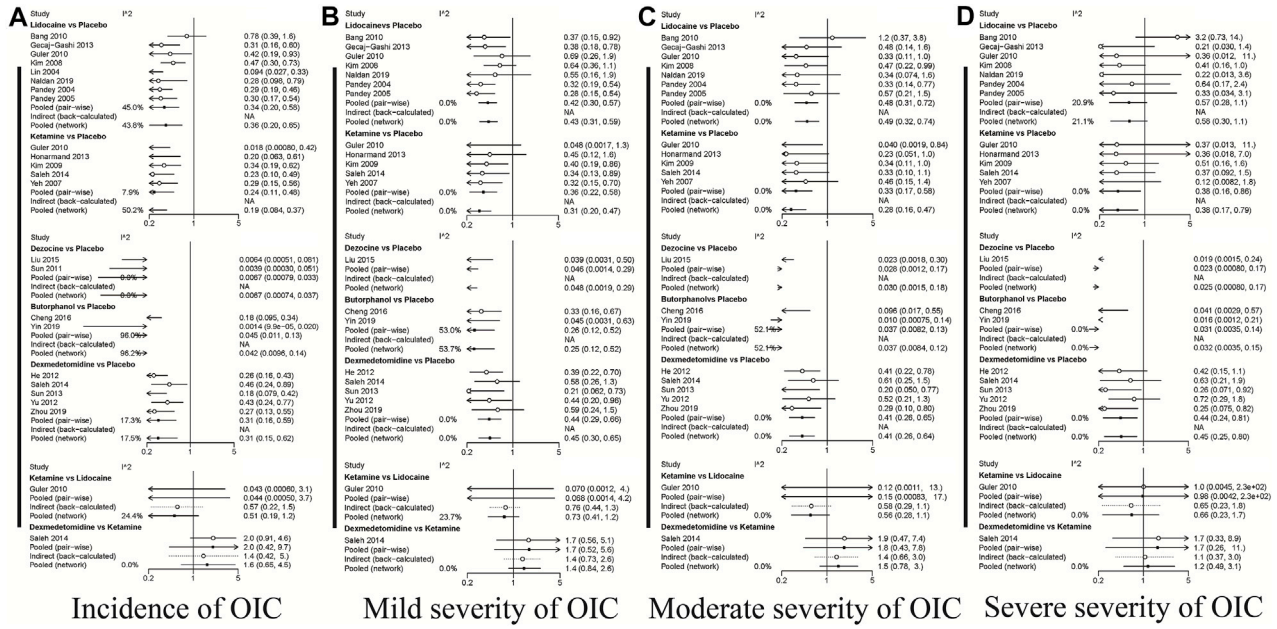

FIGURE 4 | Heterogeneity between different comparisons of drugs. **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC.

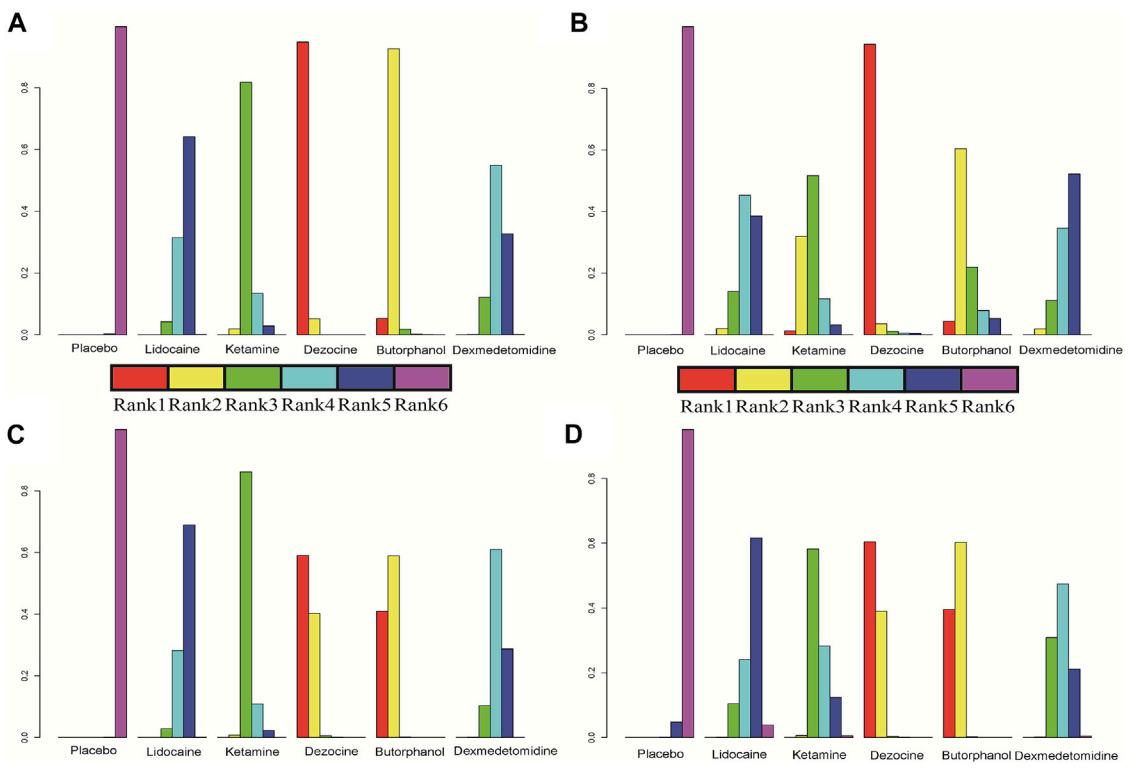

FIGURE 5 | Individual rank plot for four clinical outcomes. **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC.

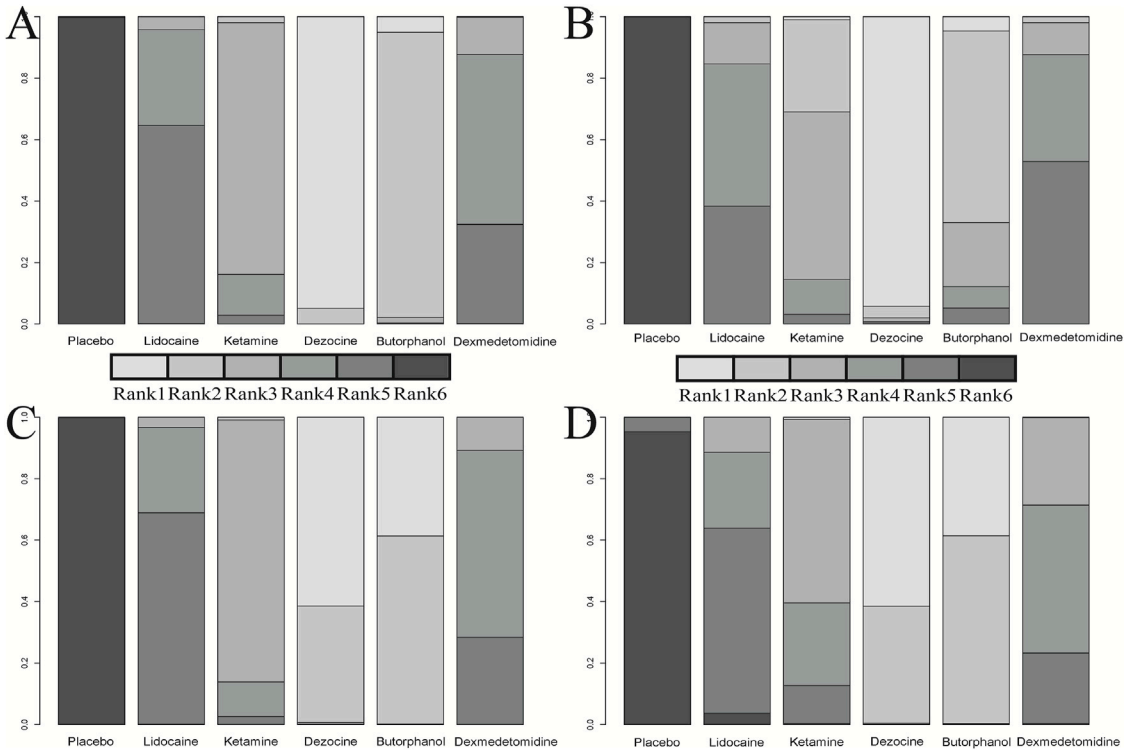

FIGURE 6 | Cumulative rank plot for four clinical outcomes. **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC.

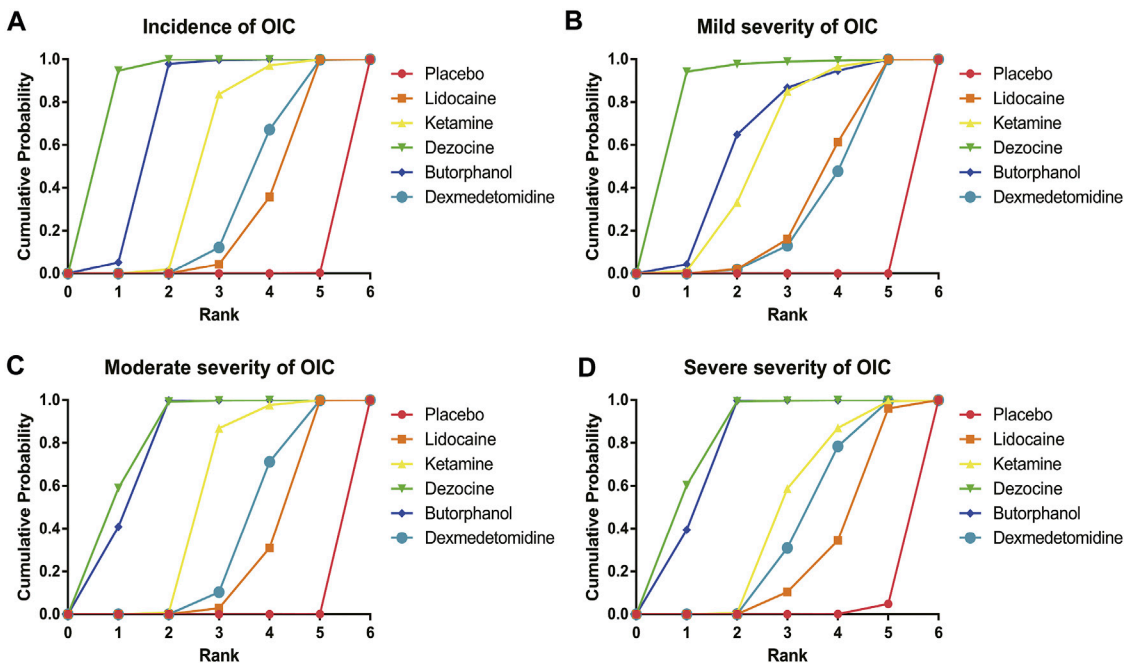

FIGURE 7 | Surface under the cumulative ranking curve (SUCRA) probabilities of different drugs for four clinical outcomes. **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC.

TABLE 2 | Surface under the cumulative ranking curve (SUCRA) probabilities of different drugs for four clinical outcomes.

Intervention	Placebo (%)	Lidocaine (%)	Ketamine (%)	Dezocine (%)	Butorphanol (%)	Dexmedetomidine (%)
Incidence of OIC	8.39	31.67	55.47	90.77	75.47	38.25
Mild severity of OIC	8.35	38.27	61.05	90.07	66.78	35.48
Moderate severity of OIC	8.35	30.63	55.90	84.70	81.80	38.62
Severe severity of OIC	9.17	31.87	49.32	84.93	81.55	43.18

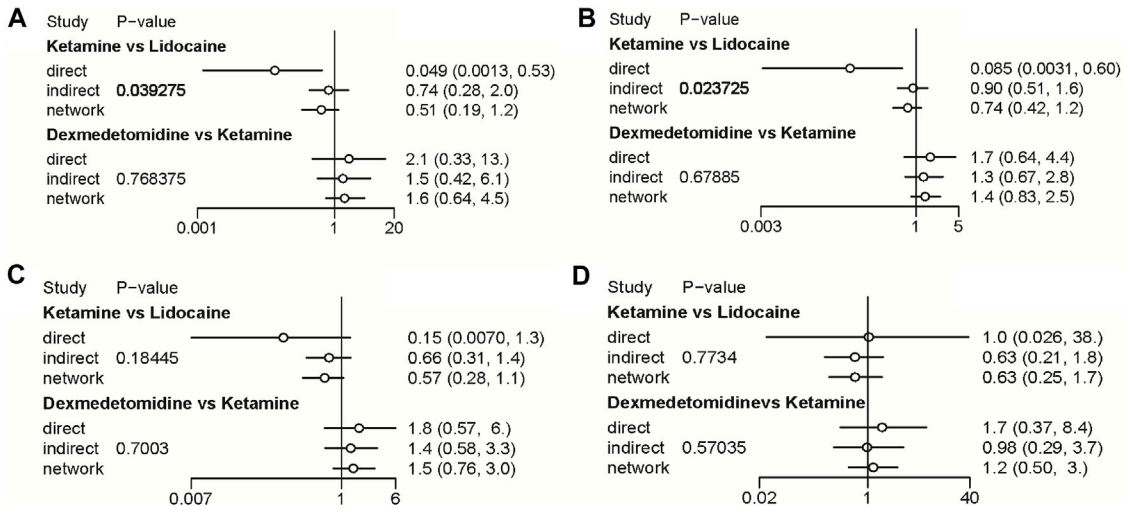

FIGURE 8 | Node-splitting method in comparisons between direct and indirect evidence. **(A)** Incidence of OIC; **(B)** Mild severity of OIC; **(C)** Moderate severity of OIC; and **(D)** Severe severity of OIC.

inhibit the moderate severity of OIC, compared with that of the placebo (all *p-values* < 0.05). Moreover, dezocine had the best effect compared with that of other five drugs (all *p-values* < 0.05). Heterogeneity between different comparisons of drugs is shown in **Figure 4C**. Similar to the results of incidence of OIC, individual and cumulative rank plots explained that the rank probability for mild severity of OIC from best to worst was dezocine, butorphanol, ketamine, dexmedetomidine, lidocaine, and placebo (**Figure 5C**, **Figure 6C**). Furthermore, their surface under the cumulative ranking curve (SUCRA) probabilities of six drugs for moderate severity of OIC are also presented in **Figure 7C**; **Table 2**. In addition, ***p***-values of the node-splitting method were all more than 0.05, indicating the consistency of the direct and indirect evidence (**Figure 8C**). Sensitivity analysis was also conducted as shown in **Supplementary Figure S4C**, indicating the robustness of our results.

Severe Severity of OIC

A total of 18 RCTs contributed to the analysis of severe severity of OIC, including six drugs (lidocaine, ketamine, dezocine, butorphanol, dexmedetomidine, and placebo). **Figure 3D**; **Supplementary Figure S3D** detailed the efficacy of different comparisons of drugs by RRs and corresponding 95% CrIs. As same as previous results, four drugs, namely, ketamine, dezocine, butorphanol, and dexmedetomidine could prevent the severe severity of OIC, compared with that of the placebo (all *p-values* < 0.05). Moreover, dezocine had the best effect compared with that of other five drugs (all *p-values* < 0.05). **Figure 4D** showed the heterogeneity between different comparisons of drugs. Similar to the results of the incidence of OIC, individual and cumulative rank plots explained that the rank probability for severe severity of OIC from first to last was dezocine, butorphanol, ketamine, dexmedetomidine, lidocaine, and placebo (**Figure 5D**, **Figure 6D**). Furthermore, the surface under the cumulative ranking curve (SUCRA) probabilities of six drugs for severe severity of OIC are also exhibited in **Figure 7D**; **Table 2**. Furthermore, *p*-values of the node-splitting method were all above 0.05, indicating the consistency of the direct and indirect evidence (**Figure 8D**). Sensitivity analysis was also conducted as shown in **Supplementary Figure S4D**, indicating the robustness of our results.

DISCUSSION

Although OIC was a transient, light, and self-limiting disease, it is a well-known adverse effect encountered during opioid administration, and pharmacologically induced cough could even be severe enough to result in death, especially for patients with comorbidities (Tweed and Dakin, 2001; Clivio et al., 2019). Therefore, there was an urgent need to take effective measures for these patients. Currently,

pharmacological interventions have been widely used in the clinical setting. Due to the absence of direct comparisons of different pharmacological interventions and the application of novel therapeutic drugs, we, as clinical physicians, often face difficulties in choosing the optimal therapeutic drug for patients for preventing OIC during administration of general anesthesia. Hence, this network meta-analysis of RCTs was conducted to provide a hierarchy of five different therapeutic drugs to provide some references for further clinical research.

In this article, a total of six drugs, namely, lidocaine, ketamine, dezocine, butorphanol, dexmedetomidine, and placebo were finally enrolled. A total of four clinical outcomes comprising incidence of OIC, mild severity of OIC, moderate severity of OIC, and severe severity of OIC were ultimately evaluated. The overall heterogeneity between different comparisons of drugs was low to moderate, except for butorphanol vs placebo. The results of traditional pair-wise meta-analyses indicated that all of the five drugs (lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine) could prevent OIC for four clinical outcomes, compared with that of the placebo. Moreover, dezocine had the best effect, compared with that of other drugs. Network meta-analysis results suggested that the rank probability for incidence of OIC, moderate severity of OIC, and severe severity of OIC from best to worst was dezocine, butorphanol, ketamine, dexmedetomidine, lidocaine, and placebo, and the rank probability for mild severity of OIC from first to last was dezocine, butorphanol, ketamine, lidocaine, dexmedetomidine, and placebo, according to individual rank plots, cumulative rank plots, and SUCRA probabilities.

Currently, the mechanisms of OIC still remain unclear. Previous studies revealed that two main mechanisms might be among the reasons for OIC. On the one hand, the activation of the parasympathetic nervous system after opioid administration, could result in cough and bronchoconstriction (Yasuda et al., 1978), and on the other hand, the pulmonary chemoreflex could be another possible mechanism, mediated by rapidly adapting receptors (irritant receptors) or vagal C-fiber receptors (juxtacapillary receptors) close to pulmonary vessels (Böhrer et al., 1990). As reported by previous research studies, dezocine, as a mixed agonist–antagonist opioid, could activate κ receptors and antagonize the μ receptors to reduce OIC with no obvious adverse effects (Liu et al., 2015). Butorphanol, also as an agonist–antagonist opioid, could not only antagonize opioid-activated μ receptors but also activate the C-fiber receptor to inhibit the cough reflex afferent pathway (Zhang et al., 2018). Lidocaine was found to be effective in reducing OIC by suppressing brain stem function or anesthetizing the peripheral cough receptors (Poulton and James, 1979). Ketamine was reported to inhibit OIC by having an antagonistic effect on N-methyl-D-aspartate (NMDA) receptors (Said et al., 1995). Dexmedetomidine, as a highly selective α2-adrenergic agonist, could also reduce OIC via activating α2-adrenergic receptors to reverse muscular rigidity or relax tracheal smooth muscle contraction induced by histamine (Groeben et al., 2004).

In consistence with previously published studies, our results shed light on the effectiveness of five therapeutic drugs (lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine) in preventing OIC. Meta-analysis of RCTs conducted by Xiong et al. reported that dezocine could significantly reduce sufentanil-induced cough during general anesthesia induction, with no significant effect on vital signs (Xiong et al., 2020). Meta-analysis of RCTs conducted by Zhang et al. explained that butorphanol could also effectively prevent the incidence and severity of OIC (Zhang et al., 2018). Meta-analysis of RCTs conducted by Sun et al. suggested the effectiveness of prophylactic intravenous lidocaine in decreasing OIC during general anesthesia induction (Sun et al., 2014). Meta-analysis of RCTs conducted by Li et al. showed that prophylactic intravenous drugs such as ketamine, lidocaine, priming of fentanyl, dexmedetomidine, dezocine, and propofol was successful in inhibiting OIC (Shuying et al., 2016). Although all of these five drugs were effective in preventing OIC, they were compared with the placebo, and direct comparisons of different pharmacological interventions were absent. In this article, we not only compared the effectiveness of five drugs but also took advantage of network meta-analysis of RCTs to provide a hierarchy of these drugs.

As for adverse effects, a high dose of lidocaine could result in arrhythmia and cardiovascular depression during general anesthesia induction (Schlimp and Wiedermann, 2005). Ketamine could lead to hallucinations and elevation of blood pressure, intraocular pressure, and intracranial pressure (Shuying et al., 2016). Dexmedetomidine had adverse effects such as hypotension and bradycardia (Ebert et al., 2000). Currently, no significant effect on vital signs had been found in administration of dezocine. Dezocine and butorphanol could mainly result in respiratory depression, postoperative nausea, and vomiting (Sun et al., 2011; Zhang et al., 2018). Interestingly, we noticed that the combination of different drugs could effectively enhance the effect of reducing OIC. Honarmand et al. explained that a combination of ketamine and dexamethasone could significantly reduce the incidence of OIC than their single use (Honarmand et al., 2013). Saleh et al. found that ketamine in combination with dexmedetomidine could also effectively suppress OIC and delay the cough onset time (Saleh et al., 2014). Yu et al. revealed similar results in the combination of dexmedetomidine and midazolam for suppressing fentanyl-induced cough (Yu et al., 2012). Subsequent research studies should pay more attention to different drug combinations and their adverse effects.

In terms of the effects of different drug doses on OIC, Cheng et al. suggested that 0.03 mg/kg butorphanol was as effective as 0.015 mg/kg butorphanol in clinical practice to suppress fentanyl-induced cough (Cheng et al., 2016). Xu et al. revealed that dezocine attenuated fentanyl-induced cough in a dose-dependent manner, and the optimal dose was 0.1 mg/kg (Xu et al., 2015). Pandey et al. identified that the minimal dose of intravenous lidocaine for suppressing OIC was 0.5 mg/kg and any increased dose could not further reduce OIC (Pandey et al., 2005). Kim et al. found that a low dose of ketamine (0.1 mg/kg) was also effective in decreasing remifentanil-induced cough without

influencing its severity and onset time (Kim et al., 2009). Zhou et al. also identified that the optimal dose of dexmedetomidine in the suppression of fentanyl-induced cough was 0.6 mg/kg, with no side effects (Zhou et al., 2019). In summary, the optimal dose of different drugs for preventing OIC needs to be fully explored.

As far as we are aware, this is the first network meta-analysis comparing the effectiveness of five therapeutic drugs (lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine) in preventing OIC, based on RCTs, which shall have a clear impact on the group baseline features and provide enough statistical power. Moreover, we not only conducted the direct comparisons of the five drugs but also performed indirect comparisons by means of network meta-analysis to provide a hierarchy of these drugs. Our analysis was anticipated to provide some references for guiding further clinical research. There were several limitations in this article too. First, the overall heterogeneity between different comparisons of drugs was low to moderate, except for butorphanol vs. placebo. Second, *p*-values of the node-splitting method between ketamine vs. lidocaine for incidence of OIC and mild severity of OIC were all below 0.05, indicating the inconsistency of the direct and indirect evidence. Third, due to the limitation of the meta-analysis, we could only use limited data obtained from previously published articles, and thus could not specify patients' baseline characteristics and demographics. Hence, we currently faced difficulties in performing network meta-regression analyses to adjust for those effect modifiers and confounders. In summary, our results were merely analyzed in consideration of effectiveness, without consideration of different doses, adverse effects, time point of drug administration, and cost-benefit analysis. Subsequent high-quality RCTs were required to pay more attention to these aspects.

CONCLUSION

Taken together, our results indicated that all of the five drugs, namely, lidocaine, ketamine, dezocine, butorphanol, and dexmedetomidine could prevent OIC for four clinical outcomes, compared with the placebo. Among them, dezocine had the best effect compared with that of other drugs. Moreover, the rank probability for the incidence of OIC, moderate severity of OIC, and severe severity of OIC from best to worst was dezocine, butorphanol, ketamine, dexmedetomidine, lidocaine, and placebo, and the rank probability for mild severity of OIC from first to last was dezocine, butorphanol, ketamine, lidocaine, dexmedetomidine, and placebo, based on the network meta-analysis results. Our analysis was anticipated to provide some references for guiding further clinical research, and subsequent high-quality RCTs were required to verify our results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

XC: Protocol/project development, data analysis, and article revision; YD: article writing/editing, data collection, or management.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.684276/full#supplementary-material

REFERENCES

Ambesh, S. P., Singh, N., Gupta, D., Singh, P. K., and Singh, U. (2010). A Huffing Manoeuvre, Immediately before Induction of Anaesthesia, Prevents Fentanyl-Induced Coughing: a Prospective, Randomized, and Controlled Study. *Br. J. Anaesth.* 104 (1), 40–43. doi:10.1093/bja/aep333

Ando, K., Akimoto, K., Sato, H., Manabe, R., Kishino, Y., Homma, T., et al. (2020). Brigatinib and Alectinib for ALK Rearrangement-Positive Advanced Non-small Cell Lung Cancer with or without Central Nervous System Metastasis: A cSystematic Review and Network Meta-Analysis. *Cancers (Basel)* 12 (4). doi:10.3390/cancers12040942

Bang, S. R., Ahn, H. J., Kim, H. J., Kim, G. H., Kim, J. A., Yang, M., et al. (2010). Comparison of the Effectiveness of Lidocaine and Salbutamol on Coughing Provoked by Intravenous Remifentanil during Anesthesia Induction. *Korean J. Anesthesiol* 59 (5), 319–322. doi:10.4097/kjae.2010.59.5.319

Böhrer, H., Fleischer, F., and Werning, P. (1990). Tussive Effect of a Fentanyl Bolus Administered through a central Venous Catheter. *Anaesthesia* 45 (1), 18–21. doi:10.1111/j.1365-2044.1990.tb14496.x

Cha, A. S., Chen, Y., Fazioli, K., Rivara, M. B., and Devine, E. B. (2021). Microvascular Benefits of New Antidiabetic Agents: A Systematic Review and Network Meta-Analysis of Kidney Outcomes. *J. Clin. Endocrinol. Metab.* 106 (4), 1225–1234. doi:10.1210/clinem/dgaa894

Cheng, X. Y., Lun, X. Q., Li, H. B., and Zhang, Z. J. (2016). Butorphanol Suppresses Fentanyl-Induced Cough during General Anesthesia Induction: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. *Medicine (Baltimore)* 95 (26), e3911. doi:10.1097/MD.0000000000003911

Clivio, S., Putzu, A., and Tramèr, M. R. (2019). Intravenous Lidocaine for the Prevention of Cough: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Anesth. Analg* 129 (5), 1249–1255. doi:10.1213/ANE.0000000000003699

Dias, S., Welton, N. J., Caldwell, D. M., and Ades, A. E. (2010). Checking Consistency in Mixed Treatment Comparison Meta-Analysis. *Stat. Med.* 29 (8), 932–944. doi:10.1002/sim.3767

Ebert, T. J., Hall, J. E., Barney, J. A., Uhrich, T. D., and Colinco, M. D. (2000). The Effects of Increasing Plasma Concentrations of Dexmedetomidine in Humans. *Anesthesiology* 93 (2), 382–394. doi:10.1097/00000542-200008000-00016

Gecaj-Gashi, A., Nikolova-Todorova, Z., Ismaili-Jaha, V., and Gashi, M. (2013). Intravenous Lidocaine Suppresses Fentanyl-Induced Cough in Children. *Cough* 9, 20. doi:10.1186/1745-9974-9-20

Groeben, H., Mitzner, W., and Brown, R. H. (2004). Effects of the Alpha2-Adrenoceptor Agonist Dexmedetomidine on Bronchoconstriction in Dogs. *Anesthesiology* 100 (2), 359–363. doi:10.1097/00000542-200402000-00026

Guler, G., Aksu, R., Bicer, C., Tosun, Z., and Boyaci, A. (2010). Comparison of the Effects of Ketamine or Lidocaine on Fentanyl-Induced Cough in Patients Undergoing Surgery: A Prospective, Double-Blind, Randomized, Placebo-Controlled Study. *Curr. Ther. Res. Clin. Exp.* 71 (5), 289–297. doi:10.1016/j.curtheres.2010.10.004

He, L., Xu, J. M., and Dai, R. P. (2012). Dexmedetomidine Reduces the Incidence of Fentanyl-Induced Cough: a Double-Blind, Randomized, and Placebo-Controlled Study. *Ups J. Med. Sci.* 117 (1), 18–21. doi:10.3109/03009734.2011.629749

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., et al. (Editors) (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd Edition. Chichester, United Kingdom: John Wiley and Sons, S38.

Honarmand, A., Safavi, M., and Khalighinejad, F. (2013). A Comparison of the Effect of Pretreatment with Intravenous Dexamethasone, Intravenous Ketamine, and Their Combination, for Suppression of Remifentanil-Induced Cough: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Adv. Biomed. Res.* 2, 60. doi:10.4103/2277-9175.115808

Kim, J. Y., Kim, J. Y., Park, S. Y., Jung, W. S., and Kwak, H. J. (2009). Effect of Low Dose Ketamine to Prevent Remifentanil-Induced Cough: a Randomized, Double-Blind, Placebo Controlled Trial. *Korean J. Anesthesiol* 56 (6), 624–627. doi:10.4097/kjae.2009.56.6.624

Kim, J. Y., Park, K. S., Kim, J. S., Park, S. Y., and Kim, J. W. (2008). The Effect of Lidocaine on Remifentanil-Induced Cough. *Anaesthesia* 63 (5), 495–498. doi:10.1111/j.1365-2044.2007.05414.x

Lin, C. S., Sun, W. Z., Chan, W. H., Lin, C. J., Yeh, H. M., and Mok, M. S. (2004). Intravenous Lidocaine and Ephedrine, but Not Propofol, Suppress Fentanyl-Induced Cough. *Can. J. Anaesth.* 51 (7), 654–659. doi:10.1007/BF03018421

Lin, J. A., Yeh, C. C., Lee, M. S., Wu, C. T., Lin, S. L., and Wong, C. S. (2005). Prolonged Injection Time and Light Smoking Decrease the Incidence of Fentanyl-Induced Cough. *Anesth. Analg* 101 (3), 670–contents. doi:10.1213/01.ANE.0000159161.31276.DB

Liu, R., Huang, X. P., Yeliseev, A., Xi, J., and Roth, B. L. (2014). Novel Molecular Targets of Dezocine and Their Clinical Implications. *Anesthesiology* 120 (3), 714–723. doi:10.1097/ALN.0000000000000076

Liu, X. S., Xu, G. H., Shen, Q. Y., Zhao, Q., Cheng, X. Q., Zhang, J., et al. (2015). Dezocine Prevents Sufentanil-Induced Cough during General Anesthesia Induction: A Randomized Controlled Trial. *Pharmacol. Rep.* 67 (1), 52–55. doi:10.1016/j.pharep.2014.08.004

Lumley, T. (2002). Network Meta-Analysis for Indirect Treatment Comparisons. *Stat. Med.* 21 (16), 2313–2324. doi:10.1002/sim.1201

Ma, L., Jin, G., Yao, K., Yang, Y., Chang, R., Wang, W., et al. (2021). Safety and Efficacy of Anti-PD-1/pd-L1 Inhibitors Compared with Docetaxel for NSCLC: A Systematic Review and Meta-Analysis. *Front. Pharmacol.* 12, 699892. doi:10.3389/fphar.2021.699892

Min, S. K., Kim, D. H., Cho, H. B., Moon, B. K., and Kim, J. Y. (2012). Limited Maximal Flow Rate of Target-Controlled Remifentanil Infusion and Induced Cough. *Anaesthesia* 67 (2), 145–148. doi:10.1111/j.1365-2044.2011.06961.x

Naldan, M. E., Arslan, Z., Ay, A., and Yayık, A. M. (2019). Comparison of Lidocaine and Atropine on Fentanyl-Induced Cough: A Randomized Controlled Study. *J. Invest. Surg.* 32 (5), 428–432. doi:10.1080/08941939.2018.1424272

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 Statement: an Updated Guideline for Reporting Systematic Reviews. *Bmj* 372, n71. doi:10.1136/bmj.n71

Pandey, C. K., Raza, M., Ranjan, R., Lakra, A., Agarwal, A., Singh, U., et al. (2004). Intravenous Lidocaine Suppresses Fentanyl-Induced Coughing: a Double-Blind, Prospective, Randomized Placebo-Controlled Study. *Anesth. Analg* 99 (6), 1696. doi:10.1213/01.ANE.0000136967.82197.82

Pandey, C. K., Raza, M., Ranjan, R., Singhal, V., Kumar, M., Lakra, A., et al. (2005). Intravenous Lidocaine 0.5 mg.Kg-1 Effectively Suppresses Fentanyl-Induced Cough. *Can. J. Anaesth.* 52 (2), 172–175. doi:10.1007/BF03027724

Peringathara, B., and Robinson, S. (2016). Fentanyl-induced Cough Is a Risk Factor for Postoperative Nausea and Vomiting. *Br. J. Anaesth.* 117 (2), 269. doi:10.1093/bja/aew207

Poulton, T. J., and James, F. M., 3rd (1979). Cough Suppression by Lidocaine. *Anesthesiology* 50 (5), 470–472. doi:10.1097/00000542-197905000-00018

Said, S. I., Berisha, H. I., and Pakbaz, H. (1995). N-methyl-D-aspartate Receptors outside the central Nervous System: Activation Causes Acute Lung Injury that Is Mediated by Nitric Oxide Synthesis and Prevented by Vasoactive Intestinal Peptide. *Neuroscience* 65 (4), 943–946. doi:10.1016/0306-4522(95)00021-a

Saleh, A. J., Zhang, L., Hadi, S. M., and Ouyang, W. (2014). A Priming Dose of Intravenous Ketamine-Dexmedetomidine Suppresses Fentanyl-Induced Coughing: a Double-Blind, Randomized, Controlled Study. *Ups J. Med. Sci.* 119 (4), 333–337. doi:10.3109/03009734.2014.968270

Schlimp, C. J., and Wiedermann, F. J. (2005). Does Fentanyl-Induced Cough Justify Pre-treatment with Iv Lidocaine 2 mg.Kg-1. *Can. J. Anaesth.* 52 (2), 207. doi:10.1007/BF03027731

Shrestha, S. K., Bhattarai, B., and Shah, R. S. (2012). Preemptive Use of Small Dose Fentanyl Suppresses Fentanyl Induced Cough. *Kathmandu Univ. Med. J. (Kumj)* 10 (40), 16–19. doi:10.3126/kumj.v10i4.10988

Shuying, L., Ping, L., Juan, N., and Dong, L. (2016). Different Interventions in Preventing Opioid-Induced Cough: a Meta-Analysis. *J. Clin. Anesth.* 34, 440–447. doi:10.1016/j.jclinane.2016.05.034

Sun, L., Guo, R., and Sun, L. (2014). The Impact of Prophylactic Intravenous Lidocaine on Opioid-Induced Cough: a Meta-Analysis of Randomized Controlled Trials. *J. Anesth.* 28 (3), 325–333. doi:10.1007/s00540-013-1732-3

Sun, S., and Huang, S. Q. (2013). Effects of Pretreatment with a Small Dose of Dexmedetomidine on Sufentanil-Induced Cough during Anesthetic Induction. *J. Anesth.* 27 (1), 25–28. doi:10.1007/s00540-012-1470-y

Sun, Z. T., Yang, C. Y., Cui, Z., Zhang, J., and Han, X. P. (2011). Effect of Intravenous Dezocine on Fentanyl-Induced Cough during General Anesthesia Induction: a Double-Blinded, Prospective, Randomized, Controlled Trial. *J. Anesth.* 25 (6), 860–863. doi:10.1007/s00540-011-1237-x

Tweed, W. A., and Dakin, D. (2001). Explosive Coughing after Bolus Fentanyl Injection. *Anesth. Analg* 92 (6), 1442–1443. doi:10.1097/00000539-200106000-00018

Valkenhoef, G. V., and Kuiper, J. (2016). *Gemtc: Network Meta-Analysis Using Bayesian Methods*. John Wiley & Sons, 76–93.

Wang, Y., Zhu, J., Qin, Z., Wang, Y., Chen, C., Wang, Y., et al. (2018). Optimal Biopsy Strategy for Prostate Cancer Detection by Performing a Bayesian Network Meta-Analysis of Randomized Controlled Trials. *J. Cancer* 9 (13), 2237–2248. doi:10.7150/jca.24690

Wu, H. Y., Huang, J. W., Lin, H. J., Liao, W. C., Peng, Y. S., Hung, K. Y., et al. (2013). Comparative Effectiveness of Renin-Angiotensin System Blockers and Other Antihypertensive Drugs in Patients with Diabetes: Systematic Review and Bayesian Network Meta-Analysis. *Bmj* 347 (2), f6008. doi:10.1136/bmj.f6008

Xiong, Z., Yi, P., Song, J., and Tan, M. (2020). Dezocine Prevents Sufentanil-Induced Cough during General Anesthesia Induction: a Meta-Analysis of Randomised Controlled Trials. *BMC Anesthesiol* 20 (1), 154. doi:10.1186/s12871-020-01076-w

Xu, Y., Zhu, Y., Wang, S., Ren, Y., and Miao, C. (2015). Dezocine Attenuates Fentanyl-Induced Cough in a Dose-dependent Manner-A Randomized Controlled Trial. *Int. J. Clin. Exp. Med.* 8 (4), 6091–6096.

Yasuda, I., Hirano, T., Yusa, T., and Satoh, M. (1978). Tracheal Constriction by Morphine and by Fentanyl in Man. *Anesthesiology* 49 (2), 117–119. doi:10.1097/00000542-197808000-00012

Yeh, C. C., Wu, C. T., Huh, B. K., Lee, M. S., Lin, S. L., J Sheen, M., et al. (2007). Premedication with Intravenous Low-Dose Ketamine Suppresses Fentanyl-Induced Cough. *J. Clin. Anesth.* 19 (1), 53–56. doi:10.1016/j.jclinane.2006.05.021

Yin, F., and Zhang, T. (2019). A Small Dose of Butorphanol Prevents Sufentanil-Induced Cough during General Anesthesia Induction. *J. Craniofac. Surg.* 30 (8), 2499–2501. doi:10.1097/SCS.0000000000005967

Yu, H., Yang, X. Y., Zhang, X., Li, Q., Zhu, T., Wang, Y., et al. (2007). The Effect of Dilution and Prolonged Injection Time on Fentanyl-Induced Coughing. *Anaesthesia* 62 (9), 919–922. doi:10.1111/j.1365-2044.2007.05147.x

Yu, J., Lu, Y., Dong, C., Zhu, H., and Xu, R. (2012). Premedication with Intravenous Dexmedetomidine-Midazolam Suppresses Fentanyl-Induced Cough. *Ir J. Med. Sci.* 181 (4), 517–520. doi:10.1007/s11845-012-0807-8

Zhang, J., Miao, S., Tu, Q., Shi, M., Zou, L., Liu, S., et al. (2018). Effect of Butorphanol on Opioid-Induced Cough: a Meta-Analysis of Randomized Controlled Trials. *Drug Des. Devel Ther.* 12, 3263–3268. doi:10.2147/DDDT.S180533

Zhang, Q., Cheng, H., Wang, Y., Tian, Y., Xia, J., Wang, Y., et al. (2019). Different Therapeutic Regimens in the Treatment of Metastatic Prostate Cancer by Performing a Bayesian Network Meta-Analysis. *Int. J. Surg.* 66, 28–36. doi:10.1016/j.ijsu.2019.04.006

Zhou, L., Shen, Y., Huang, T., Sun, Y., Alolga, R. N., Zhang, G., et al. (2021). The Prognostic Effect of Dexamethasone on Patients with Glioblastoma: A Systematic Review and Meta-Analysis. *Front. Pharmacol.* 12, 727707. doi:10.3389/fphar.2021.727707

Zhou, W., Zhang, D., Tian, S., Yang, Y., Xing, Z., Ma, R., et al. (2019). Optimal Dose of Pretreated-Dexmedetomidine in Fentanyl-Induced Cough Suppression: a Prospective Randomized Controlled Trial. *BMC Anesthesiol* 19 (1), 89. doi:10.1186/s12871-019-0765-z

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Serious Adverse Events Reporting in Phase III Randomized Clinical Trials of Colorectal Cancer Treatments: A Systematic Analysis

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Objective: The occurrence, development, and prognosis of serious adverse events (SAEs) associated with anticancer drugs in clinical trials have important guiding significance for real-world clinical applications. However, to date, there have been no studies investigating SAEs reporting in randomized clinical trials of colorectal cancer treatments. This article systematically reviewed the SAEs reporting of phase III randomized clinical trials of colorectal cancer treatments and analyzed the influencing factors.

Methods: We reviewed all articles about phase III randomized clinical trials of colorectal cancer treatments published in the PubMed, Embase, Medline, and New England Journal of Medicine databases from January 1, 1993, to December 31, 2018, and searched the registration information of clinical trials *via* the internet sites such as "clinicaltrials.gov". We analyzed the correlation between the reported proportion (RP) of SAEs in the literature and nine elements, including the clinical trial sponsor and the publication time. Chi-square tests and binary logistic regression were used to identify the factors associated with improved SAEs reports. This study was registered on PROSPERO.

Results: Of 1560 articles identified, 160 were eligible, with an RP of SAEs of 25.5% (41/160). In forty-one publications reporting SAEs, only 14.6% (6/41) described the pattern of SAEs in detail. In clinical trials sponsored by pharmaceutical companies, the RP of SAEs was significantly higher than that in those sponsored by investigators (57.6 versus 20.7%, $p < 0.001$). From 1993 to 2018, the RP of SAEs gradually increased (none (0/6) before 2000, 17.1% (12/70) from 2000 to 2009, and 34.5% (29/84) after 2009). The average RP of SAEs published in the New England Journal of Medicine (N Engl J Med), the Lancet, the Journal of the American Medical Association (JAMA), the Lancet Oncology (Lancet Oncol), and the Journal of Clinical Oncology (J Clin Oncol) was significantly higher than that published in other journals (31.9 versus 16.7%, $p = 0.030$). In the clinical trials referenced by clinical guidelines, the RP of SAEs was higher than that in non-referenced clinical trials (32.0 versus 15.9%, $p = 0.023$). Binary logistic regression analysis showed that

pharmaceutical company sponsorship, new drug research, and sample size greater than 1000 were positive influencing factors for SAEs reporting.

Conclusion: Although the RP of SAEs increased over time, SAEs reporting in clinical trials needs to be further improved. The performance, outcomes and prognosis of SAEs should be reported in detail to guide clinical practice in the real world.

Keywords: colorectal cancer, phase III clinical trial, reported proportion, real world, SAEs

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed malignancy worldwide (Fitzmaurice et al., 2017). Chemotherapy and targeted therapy play an important role in standard treatments for colorectal cancer. Fluorouracil-based adjuvant chemotherapy significantly improved the disease-free survival (DFS) and overall survival (OS) of stage II/III colorectal cancer (Group et al., 2007; André et al., 2009; Iveson et al., 2018). Combination chemotherapy with bevacizumab or cetuximab as the initial treatment significantly improved the median progression free survival (mPFS) and median overall survival (mOS) of metastatic colorectal cancer (Saltz et al., 2008; Van Cutsem et al., 2009; Qin et al., 2018). Fruquintinib and regorafenib in the 3 + line significantly prolonged the mOS and mPFS of advanced colorectal cancer (Grothey et al., 2013; Li et al., 2015; Li et al., 2018). Based on the results of clinical trials that have confirmed the efficacy of many chemotherapeutic and targeted drugs, experts have formed guidelines and consensuses to guide the diagnosis and treatment of colorectal cancer in the real world. Reporting the occurrence, development, and prognosis of adverse events (AEs), especially serious AEs (SAEs), is particularly crucial for reducing or avoiding the toxicity of regimens in real-world clinical practice, improving patients' quality of life, and decreasing the psychological and economic burden of patients. During the past 20 years, SAEs have attracted increasing attention as the number of SAEs reported to the U.S. Food and Drug Administration (FDA) increased by 2.6 times from 1998 to 2005 (Moore et al., 2007) and by 2 times from 2006 to 2014 (Sonawane et al., 2018). Guidelines indicate that clinical trials should report AEs and SAEs in a consistent manner (Wallace et al., 2016).

AEs reporting is relatively higher in cancer clinical trial publications, but the reporting quality is low. A review showed that 96% of cancer clinical studies reported AEs, but oncology-specific reporting standards were lacking (Sivendran et al., 2014). Another article reviewed 325 randomized clinical trials, all of which reported the occurrence of AEs. Nevertheless, the AEs collection and analysis methods were highly heterogeneous, and the quality of AEs reporting did not improve significantly over time (Péron et al., 2013). In addition, there was a considerable discrepancy between the final published AEs data and the sponsors' database (Scharf and Colevas, 2006). Although there have been some reviews of AEs reports, analysis of SAEs reports on colorectal cancer clinical trials is scarce, and the report proportion of SAEs in publications is unknown.

We systematically reviewed SAEs reporting from publications of colorectal cancer clinical trials, to further draw researchers' attention to SAEs reporting. The SAEs reporting was influenced by many social factors, such as regional policy, preciseness and awareness of investigators, purpose of sponsor, so this article analyzed the possible influencing factors of SAEs reporting. Because the results of phase III randomized clinical trials were the most instructive in the real world, herein we just reviewed phase III randomized clinical trials.

MATERIALS AND METHODS

This study included randomized phase III colorectal cancer clinical trials whose intervention measures contained anticancer pharmaceuticals and whose results were published in PubMed, Embase, Medline, and the New England Journal of Medicine from January 1, 1993, to December 31, 2018. We analyzed several possible factors that may affect SAEs reporting in the literature. These factors included the region where the clinical trial was conducted, the sponsor of the clinical trial, whether the trial researched new drugs, the publication date which may reflect the change of policy and awareness of investigators, factors related with the rigorous of the clinical trials such as sample size, the type of journal and whether the clinical guidelines referenced the results of the study, and factors owned by clinical trials themselves, such as treatment line, therapeutic schedule.

Literature Search Strategy

A review of citations from PubMed, Embase, Medline, and New England Journal of Medicine for studies published between January 1, 1993 and December 31, 2018, was performed to identify eligible colorectal cancer clinical trial publications for the analysis. The search terms were as follows: "colorectal cancer" [All fields] or "colon cancer" [All fields] or "rectal cancer" [All fields], and "phase 3" [All fields] or "phase III" [All fields]. We used the filters as follows: "subjects = cancer," "article type = clinical trial," "language = English," "species = humans," and "publications dates = 1/1/1993-12/31/2018." Endnote X4 (Clarivate, Philadelphia, PA, United States) was used to manage the publications. We searched the registration information of clinical trials *via* the following internet sites: http://www.clinicaltrials.gov, http://www.isrctn.com/search, http://www.anzctr.org.au, https://www.umin.ac.jp/, http://apps.who.int/en/. The inclusion criteria were as follows: 1) phase III randomized colorectal cancer clinical trials, 2) intervention

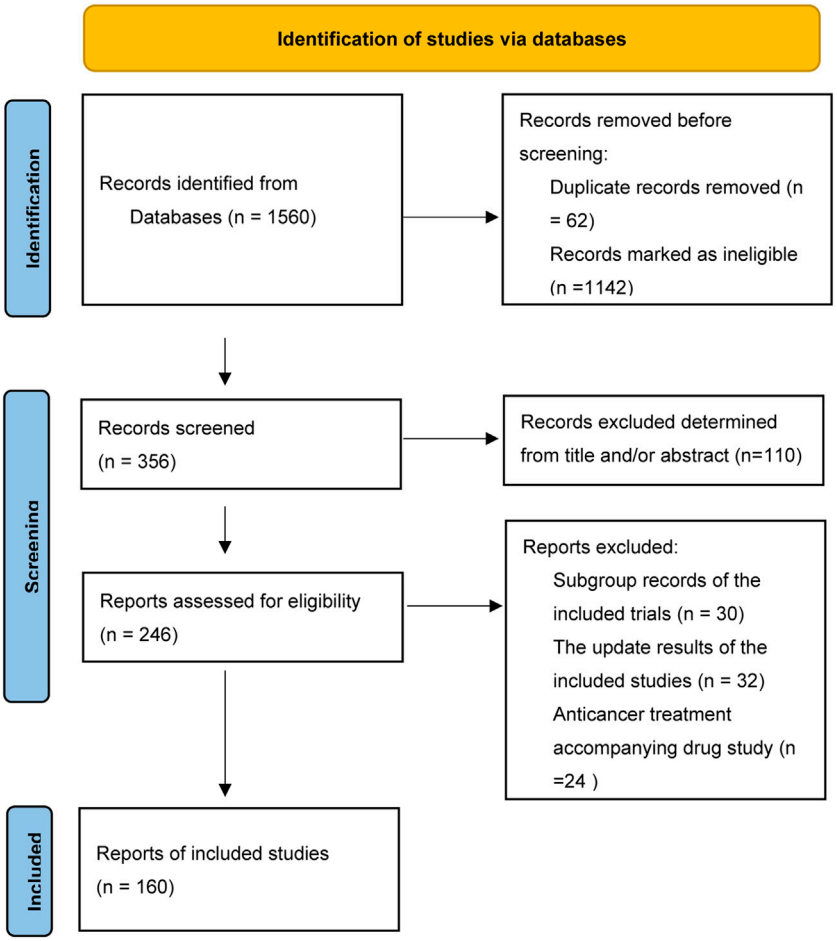

FIGURE 1 | The flowchart of the studies included in this analysis.

measure contained chemotherapy and/or target therapy, 3) the articles showed the efficacy and/or safety of the clinical trial, 4) published in English. The exclusion criteria were as follows: 1) the same research published repeatedly, 2) reviews, meta-analysis, molecular analysis and cost analysis, 3) subgroup analysis of the research already included, 4) intervention measure contained immune therapy (because the AEs spectrum of chemotherapy and immunotherapy is different), 5) clinical trials aimed to observe the efficacy or AEs of accompanying regimens along with anticancer therapy. The primary objective was the reported proportion (RP) of SAEs. The secondary objectives were the performance, outcomes and prognosis of SAEs.

$$RP\ of\ SAEs = \frac{\text{Publications that reported SAEs}}{\text{All eligible publications}} \times 100\%$$

The Criteria of AEs, SAEs and SAE Reporting

According to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.0 (Common terminology criteria for adverse events (CTCAE) v5.0, 2017), an AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Grade 3 AEs are defined as: 1) severe or medically significant but not immediately life-threatening, 2) hospitalization or prolongation of hospitalization indicated, 3) disabling, 4) limiting self-care activities of daily living (ADL). Grade 4 AEs are defined as: 1) life-threatening consequences, 2) urgent intervention indicated. Grade 5 AEs are death related to AEs.

SAEs were diagnosed according to NCI-CTC version 5.0 (Common terminology criteria for adverse events (CTCAE) v5.0, 2017) as follows:

An SAE is any untoward medical occurrence that, at any dose: 1) results in death, 2) is life-threatening, 3) an event is considered life-threatening if it is suspected that the individual is at substantial risk of dying at the time of the AEs, 4) requires inpatient hospitalization or prolongation of existing hospitalization (an admission and/or overnight stay or an event that prolongs hospitalization), 5) results in persistent or significant disability/incapacity (includes an AEs that resulted in a substantial disruption of a person's ability to conduct normal life

TABLE 1 | Characteristics of enrolled articles.

Characteristic	n	%
Region of clinical trials conducted		
Worldwide	21	13.1
Local region	139	86.9
Year of publication		
Before 2000	6	3.8
2000-2009	70	43.8
After 2009	84	52.5
Journals		
N Engl J Med	8	5.0
Lancet	9	5.6
JAMA	2	1.3
Lancet Oncol	19	11.9
J Clin Oncol	56	35.0
Ann Oncol	29	18.1
Eur J Cancer	9	5.6
Br J Cancer	7	4.4
Others	21	13.1
Sample size		
<300	40	25.0
300-999	79	49.4
≥1000	41	25.6
Treatment line		
Adjuvant/Neoadjuvant	54	33.8
First-line	81	50.6
Second-line and above	25	15.6
Total	160	

functions, i.e., significant, persistent or permanent change in, impairment of, damage to or disruption in the individual's body function/structure, physical activities, and/or quality of life), 6) is a congenital anomaly/congenital disability, 7) is medically significant (other important medical events may be considered serious when, based on appropriate medical judgment, they might jeopardize the individual and/or may require medical or surgical intervention to prevent the event from meeting a criterion for an SAE).

Herein we mainly discussed the SAEs reporting. If the publication pointed out the occurrence of SAEs, even the incidence was zero, it was judged to have reported SAEs. SAEs consisted of many events not only death, so if the publication just only reported death and didn't mention "SAEs," it wasn't judged to have reported SAEs in this review. And reporting Grade 3/4 AEs were not identified as having reported SAEs.

Data Extraction

The data were collected independently by two investigators (Yanhong Yao and Zhentao Liu) who screened eligible publications and searched the registry of clinical trials. The collected data included performance, outcomes and prognosis of SAEs, the region where the clinical trial was conducted, the sponsor of the clinical trial, whether the trial researched new drugs, the sample size, the publication date, the type of journal, whether the clinical guidelines [including the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and Chinese Society of Clinical Oncology (CSCO)] referenced the study results, the treatment lines, and treatment schedules. Professor Baoshan Cao checked the data if inconsistencies existed between the results collected by the two investigators.

Statistical Analysis

We used SPSS version 19.0 (IBM, New York, United States) to analyze the data, and differences were considered statistically significant when the two-sided p values were less than 0.05. Frequencies and percentages were calculated for counting data. The chi-square test was used to assess the association between RPs of SAEs and collected items, and Fisher's exact test was used if the theoretical number was less than 5 or the sample size was less than 40. A binary logistic regression model was used to identify items associated with SAEs reporting. The dependent variable was whether reported SAEs, and the independent variables were the positive influencing factors for SAEs reporting based chi-square test. The method of the independent variables entering the regression equation was "Backwald".

RESULTS

Characteristics of Selected Publications

From the 1560 publications initially collected by the two investigators, a total of 160 publications (**Supplementary Material**) were included in this analysis according to the eligible criteria (**Figure 1**). The characteristics of the 160 included publications were listed in **Table 1**. There were more trials conducted in local region (139, 86.9%) than worldwide (21, 13.1%). Ninety-four (58.8%) articles were published in journals such as N Engl J Med, Lancet, JAMA, Lancet Oncol and J Clin Oncol, and one hundred fifty-four (96.3%) articles were published after 2000. The sample size of one hundred and twenty (75.0%) articles was greater than 300. One hundred and six (66.2%) clinical trials researched treatment of metastatic colorectal cancer.

The Performance, Outcomes and Prognosis of SAEs

Forty-one (25.5%) of the 160 included publications reported SAEs (**Table 2**). Only six publications described the performance of SAEs in detail. None described the detailed treatment process for the SAEs. All of the publications that reported SAEs listed grade 3/4 AEs (**Table 3**). Grade 3/4 hematological toxicity (40/41) and gastrointestinal reactions (37/41) were the most common. Hypertension, proteinuria, and gastrointestinal perforation were more common for anti-vascular drugs. Hand-foot syndrome (HFS) was more common for capecitabine and regorafenib. Skin reactions were more common for cetuximab and panitumumab.

Of the forty-one publications that reported SAEs, forty publications reported whether the SAEs resulted in death, and thirty-seven publications reported the relationship between death and the treatment, and only fifteen reported the relationship between the non-death SAEs and the

TABLE 2 | The articles reported SAEs.

Clinical Trial Register No.	Authors (Year of publication)	Comparative Regimens	Sample size	Reported proportion of SAE
NCT00335595	Eduardo et al. (2012)	XELOX + Bev/Bev	480	14%/20%
NCT00719797	Loupakis et al. (2014)	FOLFIRI + Bev/FOLFOXIRI + Bev	508	19.7%/20.4%
NCT00154102	Van Cutsem et al. (2009)	FOLFIRI + Cet/FOLFIRI	1198	26%/19.3%
NCT00749450/ ISRCTN59757862	Iveson et al. (2018)	Oxaliplatin-Fluoropyrimidine 3 month/6 month	6088	14%/16%
NCT00724503/ NCT01721954	Wasan et al. (2017)	FOLFOX/FOLFOX + SIRT	1102	43%/54%
ISRCTN45133151	Kerr et al. (2016)	Capecitabine + Bev/Capecitabine	1941	30%/20%
NCT01584830	Li et al. (2015)	Regorafenib + BSC/Placebo + BSC	204	32%/26%
NCT00700102	Bennouna et al. (2013)	Bev + Chemotherapy/Chemotherapy	409	32%/33%
NCT00484939	Cunningham et al. (2013)	Bev + Capecitabine/Capecitabine	280	30%/31%
NCT01996306	Xu et al. (2018)	XELIRI ± Bev/FOLFIRI ± Bev	650	15%/20%
NCT00112918	De Gramont et al. (2012)	FOLFOX or XELOX + Bev/FOLFOX	2867	26%, 25%/20%
NCT01103323	Grothey et al. (2013)	Regorafenib/Placebo	760	44%/40%
NCT00005586/ ISRCTN82375386	QUASAR Collaborative Group et al. (2007)	Fu/Observe	3,239	0.5%/0.25%
NCT02314819	Li et al. (2018)	Fruquintinib/Placebo	404	15.5%/5.8%
NCT01955837	Xu et al. (2018)	Trifluridine or Tipiracil (TAS-102)/Placebo	406	23.2%/23.0%
NCT01228734	Qin et al (2018)	Cet + FOLFOX4/FOLFOX4	553	19.1%/13.1%
NCT00724503	Van Hazel et al. (2016)	mFOLFOX6 ± Bev/mFOLFOX6 ± Bev + Radiation	530	41.6%/54.1%
NCT00384176	Schmoll et al. (2012)	FOLFOX + Cediranib/FOLFOX + Bev	1422	39%/33%
NCT00399035	Hoff et al. (2012)	Cediranib + FOLFOX or CAPOX/Placebo + FOLFOX or CAPOX	1076	40.8%/29.3%
NCT00056459	Hecht et al. (2011)	PTK787/ZK 222584 + FOLFOX4/Placebo + FOLFOX4	1168	46.8%/38.2%
NCT00056446	Van Cutsem et al. (2011)	FOLFOX4+ PTK787/ZK 222584/FOLFOX4+Placebo	855	45.0%/34.5%
NCT00339183	Peeters et al. (2010)	FOLFIRI + Pan/FOLFIRI	1186	WT41%/31% MT37%/30%
NCT00364013	Douillard et al. (2010)	FOLFOX/FOLFOX + Pan	1096	WT36%/40% MT29%/47%
NCT00063141	Sobrero et al. (2008)	CPT11/CPT11 + Cet	1298	22.6%/29.2%
NCT00069121	Schmoll et al. (2007)	XELOX/FOLFOX	1886	22.1%/24.6%
NA	Porschen et al. (2007)	CAPOX/FOLFOX	476	21%/24%
NCT00004885	Kohne et al. (2005)	IRI + FuFA/FuFA	430	8%/3%
NA	Tournigand et al. (2004)	FOLFIRI Followed by FOLFOX6 or the Reverse Sequence	220	First line14%/5% Second line 6%/4%
NA	Saini et al. (2003)	LV5Fu2/mFULU	905	4.6%/5.1%
NCT00115765	Hecht et al. (2009)	FOLFOX or FOLFIRI + Bev/LFOX or FOLFIRI + Bev + Pan	1053	Panitumumab-related 19%
NCT01661270	Li et al. (2018)	Aflibercept + FOLFIRI/Mixed strategy/Placebo + FOLFIRI	332	20%/13%/15%
NCT01030042	Cascinu et al. (2017)	IRI + Cet Folllowed by FOLFOX or the Reverse	110	18%/10%
NA	Köhne et al. 2013	5-Fu/FA + high dose Fu	1601	14.5%/15.8%
ISRCTN2194324	Popova et al. (2008)	FuLV/Raltitrexed	1921	18.3%/16.3%
NCT00642577	Guan et al. (2011)	mIFL/mIFL + Bev	214	18.6%/10%
ACTRN12610 000148077	Papadimitriou et al. (2011)	FOLFIRI/LV5Fu2	873	27%/18%
NCT02149108	Van Cutsem et al. (2018)	Nintedanib/Placebo	768	39%/35%
NCT00646607	Lonardi et al. (2016)	FOLFOX4/XELOX	3,759	4.2%/5.6%
NCT00720512	Masi et al. (2015)	FOLFIRI/FOLFOX + Bev	185	7%/7%
NA	Fields et al. (2009)	Fu/Fu + Edrecoloma	1839	26%/26%
NCT00143403	Ychou et al. (2009)	FuLV/FOLFIRI	153	6%/13%

Abbreviation: NA, not available; Bev, bevacizumab; Pan, panitumumab; Cet, cetuximab; Fu, fluorouracil; CPT11, irinotecan; LV, leucovorin; FA, folinic acid; XELOX, oxaliplatin + capecitabine; CAPOX, oxaliplatin + capecitabine; FOLFOX, bolus and infusional fluorouracil/leucovorin + oxaliplatin; FOLFIRI, bolus and infusional fluorouracil/leucovorin; FOLFOXIRI, bolus and infusional fluorouracil/leucovorin + oxaliplatin + irinotecan; XELIRI, irinotecan + capecitabine; IFL, fluorouracil + leucovorin + irinotecan; SIRT, selective internal radiotherapy; BSC, best supportive care; PTK787 ZK: an Oral Vascular Endothelial Growth Factor Receptor Inhibitor; WT, wide-type; MT, mutant.

anticancer treatment. The proportion of deaths caused by SAEs was as follows: less than 1% in nineteen clinical trials, 1–5% in sixteen clinical trials, and 5–10% in five clinical trials. Six publications reported whether the SAEs were life-threatening, and only two publications reported the prognosis of SAEs in detail (**Figure 2**).

Analysis of the RP of SAEs

Chi-square tests (**Table 4**) showed that the RP of SAEs in clinical trials conducted worldwide (52.4% [11/21]) was higher than conducted in local region (21.6% [30/139], $p = 0.003$, **Figure 3A**). The RP of SAEs was more than twice in clinical trials sponsored by pharmaceutical companies (57.6% [19/33])

TABLE 3 | Details of Grade 3/4 AEs in the articles reported SAEs.

Comparative Regimens/AEs	Haema-AEs	FN	Infection	GIR	Liver injury	GIP	TEE	Hyper-tension	Cardio-toxicity	Haem-orrhage	Hema-turesis	Protein-uria	WHC	SNP	HFS	Asthenia	Cutire-action	Anap-hylaxis	Dysp-noea
Regorafenib/Placebo	+			+	+			+				+		+	+		+		+
Bev + Chemotherapy/ Chemotherapy	+		+	+		+	+	+		+				+		+			+
FOLFOX-4/XELOX	+	+		+										+		+		+	
FOLFIRI + Cet/FOLFIRI	+			+													+		
FOLFOX/IRI + Cet	+		+	+	+									+		+	+		
CPT11/CPT11+Cet	+			+												+	+		
FU/FU + Edrecoloma	+			+												+	+		
3 versus 6 months of adjuvant oxa-fluoropyrimidine	+													+	+		+		
Regorafenib + BSC/ Placebo + BSC	+		+		+			+	+	+		+			+		+		
FOLFOX + Pan/FOLFOX	+	+		+			+							+			+		
FOLFIRI followed by FOLFOX6 or the Reverse Sequence	+	+		+										+			+		
FOLFOX, FOLFIRI + Bev/ FOLFOX or FOLFIRI + Bev + Pan	+		+	+			+	+									+		
FOLFIRI + Pan/FOLFIRI	+	+		+			+										+		
Cet + FOLFOX-4/ FOLFOX-4	+			+													+		
FOLFIRI + Bev/ FOLFOXIRI + Bev	+	+		+			+	+						+		+			
FOLFOX4+PTK/ZK/ FOLFOX4+Placebo	+			+				+				+				+			
Bev + Capecitabine/ Capecitabine	+			+			+	+	+	+						+			
Trifluridine/Tipiracil(TAS-+02)/placebo	+		+	+	+			+								+			
FU/LV/FOLFIRI	+			+												+			
FOLFOX or XELOX + Bev/FOLFOX	+					+	+	+		+			+	+	+				
XELOX + Bev/Bev	+			+		+	+	+	+	+		+		+	+				
Cediranib + FOLFOX/ CAPOX/Placebo + FOLFOX/CAPOX				+				+						+	+				
LV5FU2/mFU/LV	+	+	+	+			+							+	+				
XELOX/FOLFOX	+	+		+										+	+				
Capecitabine + Bev/ Capecitabine	+			+		+	+	+		+		+	+		+				
XELIRI ± Bev/FOLFIRI ± Bev	+	+	+	+		+	+	+		+		+			+				
Fruquintinib vs Placebo	+		+	+	+			+		+		+			+				
FUFA/FOLFIRI	+	+		+				+							+				
FOLFOX + CEDIRANIB/ FOLFOX + Bev	+			+		+	+	+		+		+		+					
Nintedanib/Placebo	+		+	+	+			+		+		+		+					

(Continued on following page)

TABLE 3 | (*Continued*) Details of Grade 3/4 AEs in the articles reported SAEs.

Comparative Regimens/AEs	Haema-AEs	FN	Infection	GIR	Liver injury	GIP	TEE	Hyper-tension	Cardio-toxicity	Haem-orrhage	Haema-turesis	Protein-uria	WHC	SNP	HFS	Asthenia	Cutire-action	Anap-hylaxis	Dysp-noea
FOLFOX/FOLFOX + SIRT	+	+		+	+		+			+				+	+				
mFOLFOX6 ± Bev/ mFOLFOX6 ± Selective Internal Radiation	+	+		+	+		+								+				
FOLFIRI/LV5FU2	+	+		+	+										+				
PTK787/ZK 222584 +FOLFOX4/Placebo + FOLFOX4	+			+			+	+							+				
mIFL/mIFL + Bev	+	+		+		+	+	+		+		+							
Aflibercept + FOLFIRI/ Placebo + FOLFIRI	+			+				+		+		+							
FOLFIRI/FOLFOX + Bev	+			+		+	+	+		+	+								
Fu/Observe	+			+															
CAPOX/FUFOX	+																		
FU/LV/Tomudex	+	+		+															
Bolus 5-FU/FA HD-FU	+			+											+				

Abbreviation: AEs, adverse events; SAE, serious adverse events; Bev, bevacizumab; Pan, panitumumab; Cet, cetuximab; Fu, fluorouracil; CPT11, irinotecan; LV, leucovorin; FA, follinic acid; XELOX, oxaliplatin + capecitabine; CAPOX, oxaliplatin + capecitabine; FOLFOX, bolus and infusional fluorouracil/leucovorin + oxaliplatin; FOLFIRI, bolus and infusional fluorouracil/leucovorin; FOLFOXIRI, bolus and infusional fluorouracil/leucovorin + oxaliplatin + irinotecan; XELIRI, irinotecan + capecitabine; IFL, fluorouracil + leucovorin + irinotecan; SIRT, selective internal radiotherapy; BSC, best supportive care; PTK787 ZK: an oral vascular endothelial growth factor receptor inhibitor; Haema-AEs, haematological adverse events; FN, febrile neutropenia; GIR, gastrointestinal reaction; GIP, gastrointestinal perforation; TEE, thromboembolic events; WHC, wound-healing complications; SNP, sensory neuropathy; HFS, hand food syndrome.

as much as sponsored by investigators (20.7% [17/82], $p < 0.001$). Clinical trials examining new drugs (45.5% [25/55]) liked to report SAEs more than those not examining new drugs (15.2% [16/105], $p < 0.001$). Clinical trials with larger sample sizes (≥1000, 43.9% [18/41]) seemed to have a greater RP of SAEs than those with medium sample sizes (300–999, 20.3% [16/79], p =0.006) and small sample sizes (<300, 17.5% [7/40], $p = 0.010$, **Figure 3B**). The RP of SAEs increased over time. The RP of SAEs in articles published after 2009 (34.5% [29/84]) was higher than that published from 2000 to 2009 (17.1% [12/70], $p = 0.015$) and published before 2000 (none [0/6], $p = 0.171$, **Figure 3C**). The RP of SAEs in clinical trials whose results were referenced by the guidelines (32.0% [31/97]) was greater than that not referenced by guidelines (15.9% [10/63]) ($p = 0.023$). The RPs of SAEs in studies published in famous journals were as follows: 25% [2/8] in N Engl J Med, 22.2% [2/9] in Lancet, 42.1% [8/19] in Lancet Oncol, 50.0% [1/2] in JAMA and 30.4% [17/56] in J Clin Oncol (**Figure 4**), with an average RP of SAEs of 31.9% (30/94), which was significantly higher than that in studies published in other journals (16.7%, [11/66], $p = 0.030$). The RP of SAEs was significantly higher in clinical trials about second line and above treatment than those about first line and adjuvant/neoadjuvant treatment, and higher in clinical trials researched targeted therapy ± chemotherapy than those researched other therapeutic schedules (**Table 4**).

After adjusting for the nine factors, logistic regression analysis showed that pharmaceutical company sponsorship, new drug research and a sample size greater than 1000 were positive influencing factors for SAEs reporting (**Table 5**).

DISCUSSION

The registration rate of oncology clinical trials has significantly increased since 2005 (Song and Kim, 2020), and the number of clinical trials for anticancer drugs has also increased in the past decade in China (Li et al., 2019). The China Food and Drug Administration (CFDA) has issued a series of innovations to accelerate new agent approvals in oncology (Wang, 2017). Randomized phase III clinical trials are considered to be the gold standard in clinical practice. Therefore, clinical trials and SAEs reports lay the foundation for selecting anticancer treatments and managing AEs in real-world practice. Chemotherapy and targeted therapy are still mainstream treatments in colorectal cancer, one of the most common malignancies worldwide. Safety is one of the leading factors in clinical decision-making, affecting patient quality of life and the benefit-risk ratio.

This article retrospectively analyzed 160 publications that met the inclusion criteria and showed that the RP of SAEs in phase III colorectal cancer clinical trials was only 25.5%, significantly lower than that of AEs, which was reported to be 96% in cancer clinical trials in a retrospective study (Sivendran et al., 2014). One of the reasons for the low RP of SAEs was insufficient attention to SAEs reports. Some researchers believed that systematic and complete SAEs reporting increased the workload and costs when the purpose of a clinical trial was only to verify drug efficacy

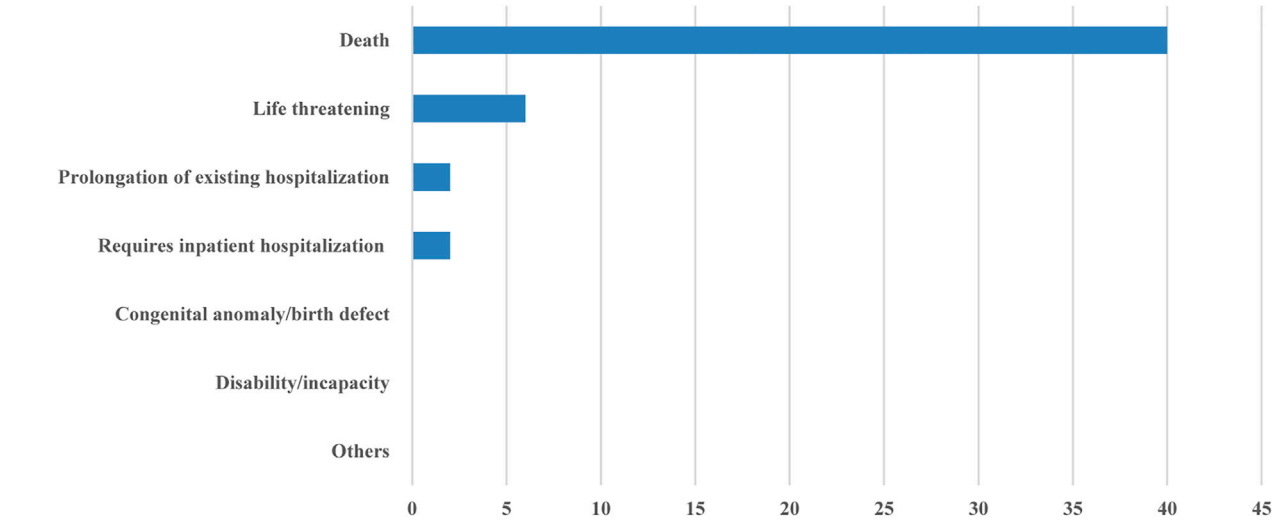

FIGURE 2 | Number of publications reported the outcomes of SAEs.

TABLE 4 | Analysis of the influencing factors of SAEs reporting.

Characteristic	Trials	Trials reported SAEs	RP of SAEs (%)	*p* Value
Total	160	41	25.5	
Region of clinical trials				
Worldwide	21	11	52.4	Reference
Local region	139	30	21.6	0.003
Trial sponsor				
Pharmaceutical Company	33	19	57.6	Reference
Investigator	82	17	20.7	<0.001
Unknown	45	5	11.1	<0.001
New drug study				
Yes	55	25	45.5	Reference
No	105	16	15.2	<0.001
Sample size				
≥1000	41	18	43.9	Reference
300-999	79	16	20.3	0.006
<300	40	7	17.5	0.010
Year of publication				
After 2009	84	29	34.5	Reference
2000-2009	70	12	17.1	0.015
Before 2000	6	0	0	0.171
N Engl J Med, Lancet, Lancet Oncol, JAMA, J Clin Oncol				
Yes	94	30	31.9	Reference
No	66	11	16.7	0.030
Referenced by Guidelines				
Yes	97	31	32.0	Reference
No	63	10	15.9	0.023
Treatment line				
Second-line and 2nd +	25	11	44.0	Reference
First-line	81	18	22.2	0.033
Adjuvant/Neoadjuvant	54	12	22.2	0.048
Therapeutic schedule				
Targeted therapy ± Chemotherapy	63	23	36.5	Reference
Chemotherapy ± Others	97	18	16.7	0.011

Abbreviation: RP, Report Proportion; SAEs, Serious Adverse Events.

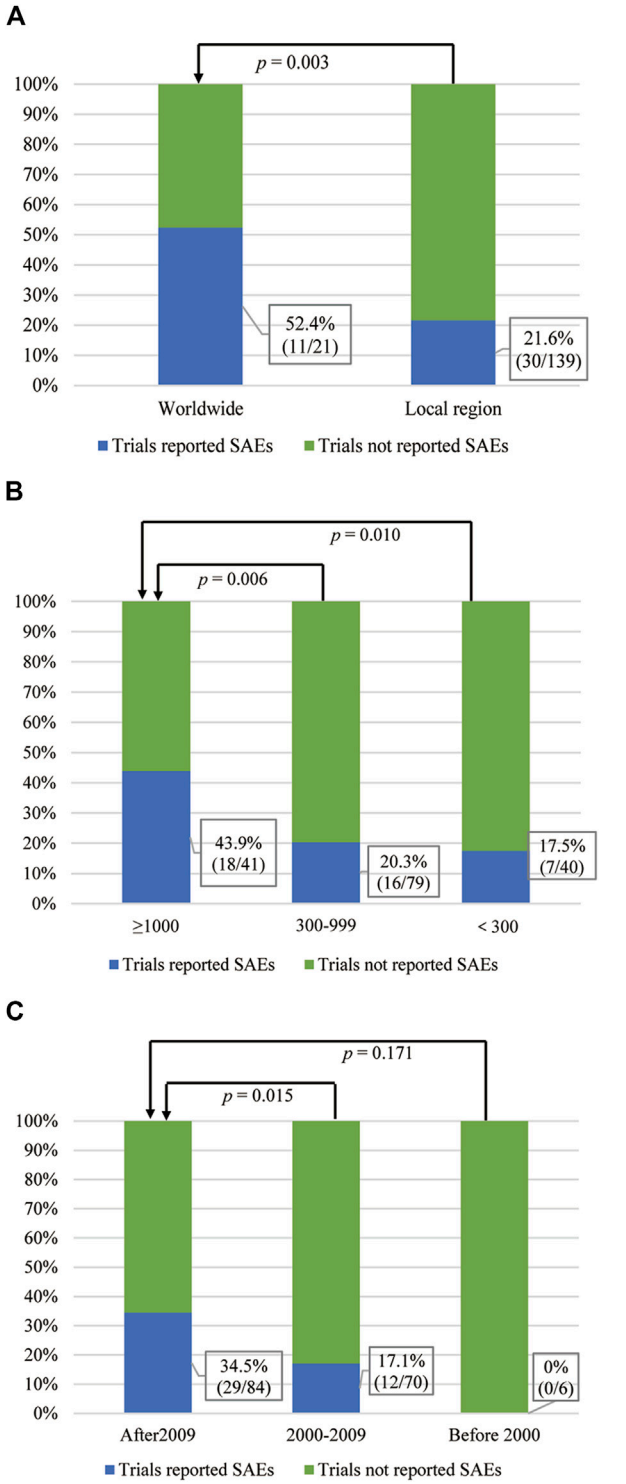

FIGURE 3 | The correlation between the RP of SAEs and the influencing factors. **(A)** Region where clinical trials conducted and SAEs reported status. **(B)** Sample size and SAE reported status. **(C)** Publication time and SAEs reported status.

(Wallace et al., 2016). Therefore, inadequate research funding was the other reason (Wallace et al., 2016).

Most publications included in this article did not report the type or prognosis of SAEs in detail. This was similar to a study examining the quality of SAEs reporting to sponsors by investigators from all clinical trials performed at Limoges University Hospital in 2012 (Crépin et al., 2016). In this study, 3.6% of the reports did not describe the seriousness of the SAEs, 9.3% were missing a causality assessment, and the date of SAEs onset was not mentioned in 5.7% of the reports. This phenomenon may be due to the lack of standard guidelines for SAEs reporting in clinical trials. On the other hand, the journal's word count requirements may limit the author's ability to provide a detailed SAEs description. The severity and duration of SAEs directly affect the prognosis and quality of life of patients, and both are essential factors for SAEs reports (Sartor, 2017). Detailed descriptions of the manifestation, severity, duration, and outcome of SAEs in phase III clinical trials, whose results have important reference value for clinical guidelines, have crucial guiding significance for real-world clinical practice. Therefore, in the future, journals about SAEs and SAEs case reports should be established for reporting SAEs in detail to better guide clinical practice and drug research and development, thereby improving cancer treatments and maximizing the benefits of patients.

The manifestations of AEs in patients with colorectal cancer were related to the drugs. The skin reactions reported in this article were more common for anti-EGFR antibodies, such as cetuximab and panitumumab, which was similar to previous reports. Some reviews and phase II clinical trials showed that the incidence of AEs and grade 3/4 AEs were 66.7% (Lynch et al., 2007) and 8%-16% (Soeda et al., 2014; Soda et al., 2015), respectively, for patients treated with cetuximab and 74.7% (Bouché et al., 2019) and 9%-15% (Nishi et al., 2016; Munemoto et al., 2018), respectively, for panitumumab. HFS was more common for regorafenib and capecitabine in this study. It has been reported that the incidence of HFS and grade 3/4 HFS were 65–69% and 15–16%, respectively, for regorafenib (Bekaii-Saab et al., 2019), and the incidence of grade 3/4 HFS for capecitabine was 8% (Soda et al., 2015) in non-phase III clinical trials. This study showed that regorafenib was related to hypertension and dyspnea, whose previously reported incidences were 62%–70% and 19%–23%, respectively, and the incidences above grade 3 were 7%–15% and 4%–6%, respectively (Bekaii-Saab et al., 2019). The incidences of hypertension, proteinuria, gastrointestinal perforation, and thrombosis were more common for bevacizumab, which was consistent with the results of many phase II clinical trials (Chen et al., 2006; Horita et al., 2011; Hong et al., 2012; Nakayama et al., 2012).

The chi-square analysis in this study showed that the RP of SAEs in clinical trials conducted worldwide (52.4%) was higher than that in those conducted in local region (21.6%). The worldwide clinical research is supervised and reviewed by an international ethics committee and global regulatory agencies. The management system is stricter, so the reporting of SAEs is more stringent. In addition, clinical

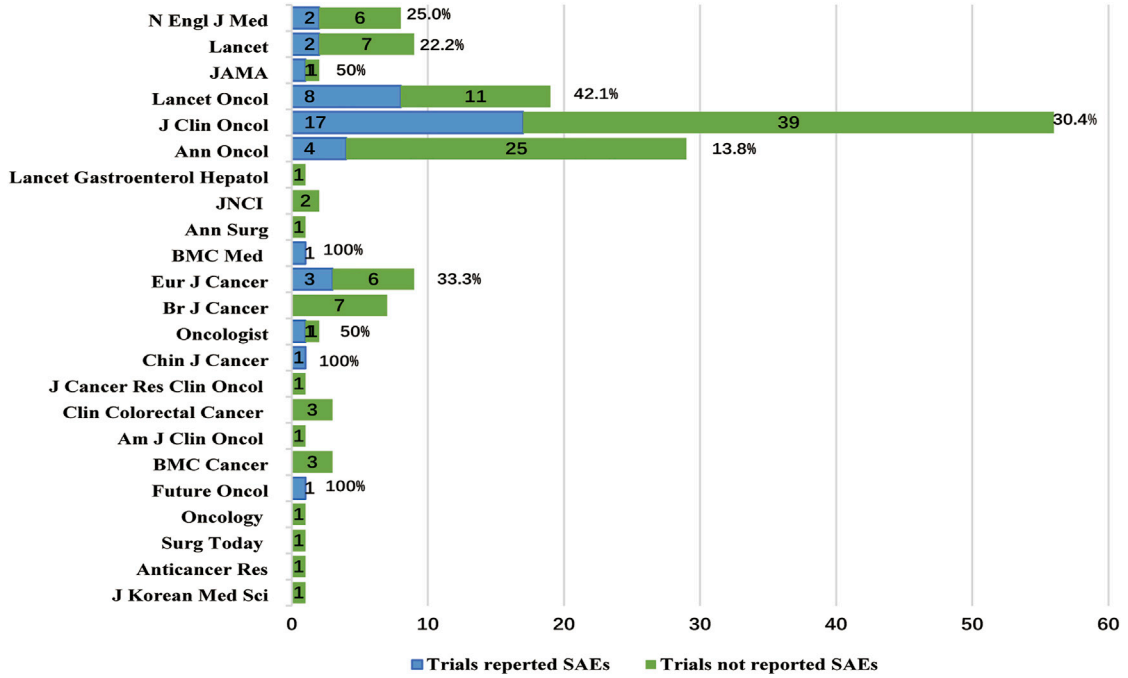

FIGURE 4 | Journals and SAEs reported status.

TABLE 5 | Binary logistic regression analysis of influencing factors of SAEs reporting.

Characteristic	Regression coefficient β	Standard error	Wald	Sig	Exp(B)	Exp(B) (95%CI)
Trial sponsor						
Pharmaceutical Company	Reference					
Investigator	−1.304	0.481	7.352	0.007	0.271	0.106–0.697
Unknown	−1.478	0.670	4.859	0.028	0.228	0.061–0.849
New drug study						
Yes *vs* No	−1.128	0.450	6.284	0.012	0.324	0.134–0.782
Sample size						
≥1000	Reference					
300-999	−1.059	0.476	4.955	0.026	0.347	0.136–0.881
<300	−1.120	0.580	3.730	0.053	0.326	0.105–1.017
Year of publications						
After 2009	Reference					
2000-2009	−0.833	0.506	2.714	0.099	0.435	0.161–1.171
Before 2000	−19.719	16,407	0.0	0.999	0	0
Referenced by Guidelines						
Yes *vs* No	2.063	0.887	5.415	0.020	7.872	0.181–1.900
Therapeutic schedule						
Targeted therapy ± Chemotherapy *vs* Chemotherapy ± Others	1.241	0.870	2.034	0.154	3.458	0.628–19.029

Abbreviation: SAEs, serious adverse events.

studies conducted in only one country had various reports of SAEs. The RP of SAEs was higher in China, Spain, Italy, and Greece, at 75, 50, 50, and 33.3%, respectively (**Figure 5**). This may be related to the differences in supervision and management of clinical research in different regions and the differences in policies and regulations.

The RP of SAEs in new drug clinical research (45.5%) was significantly higher than that in non-new drug clinical studies (15.2%) ($p < 0.001$). In addition to the effectiveness of new drugs, the safety of new drugs was of paramount concern, so the RP of SAEs was higher. Non-new drug research mainly compared the efficacy of different treatment regimens and paid less attention to SAEs, and the RP of SAEs was lower. The SAEs reporting rate of clinical studies initiated by pharmaceutical companies (57.6%) was higher than that of investigators (20.7%) ($p < 0.001$). Among 33 clinical studies

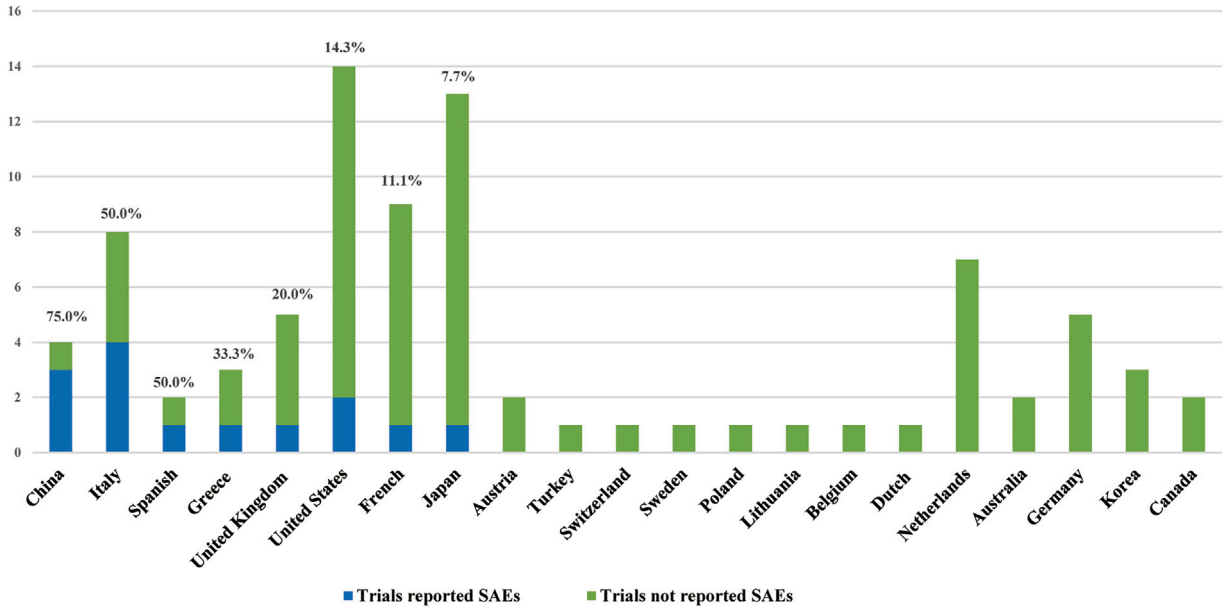

FIGURE 5 | Countries and SAEs reported status.

initiated by pharmaceutical companies, 69.7% (23) were new drug-related clinical studies, while only 39% (32 of 82) of clinical studies undertaken by investigators were new drug studies. The RP of SAEs in new drug clinical research was higher, so the RP of SAEs in clinical research initiated by pharmaceutical companies was higher. This was also the reason why the RP of SAEs was higher in clinical trials about second line and above treatment, and higher in targeted therapy based clinical trials.

This study showed that the RP of SAEs increased in the past 26 years, which may be attributed to the following. First, the National Health and Medical Research Council has provided increasingly rigorous regulations about how SAEs should be reported (Wallace et al., 2016). Second, the increasing attention paid to drug research safety has promoted the monitoring and management of data for clinical trials (Bhattacharyya et al., 2018). Pharmaceutical companies and journal editors have made recommendations on AEs (including SAE) reporting after a thorough discussion on how policies and guidelines were followed, what challenges existed, and how challenges should be addressed to improve AEs and SAEs reporting in clinical research publications to enhance the degree of authenticity and accuracy of clinical trial data (Lineberry et al., 2016). Third, the training recommendations in the Good Clinical Practice (GCP) guidelines require investigators and study coordinators executing a clinical trial to undergo training on GCP principles every 3 years (Shanley et al., 2017), enhancing investigators' compliance with GCP (Kuusisto et al., 2011). Finally, SAEs reports are processed by an automated computer system instead of personal reports with the development of information technology, saving workforce resources and time and facilitating the analysis of reporting performance and the nature of SAEs reports (London et al., 2009; Pecoraro and Luzi, 2011). AEs capture and management systems for cancer clinical trials were set up to administer and manage clinical trials, improving the efficiency, accuracy, and safety of AEs reports (Lencioni et al., 2015).

The top five journals for RPs of SAEs were N Engl J Med, Lancet, Lancet Oncol, JAMA, J Clin Oncol, with an average RP of SAEs 31.9%, which was significantly higher than that of other journals (16.7%, $p = 0.030$). This was affected by the journal's requirements. For example, Lancet has provided readers with links to websites that published clinical trial protocols since 2009, and J Clin Oncol has disclosed agreements that were previously only open to journal editors and reviewers since 2011 (Song and Kim, 2020). The improvement of clinical trial transparency is beneficial to the authenticity of clinical research data.

Patients in some clinical trials completed electronic surveys regarding symptomatic AEs according to the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (Hagelstein et al., 2016) of the National Cancer Institute (NCI) during cancer treatment, which was demonstrated to be both feasible and informative (Chung et al., 2019). A pooled analysis showed that in oncology clinical trials, PRO and AEs reports had a different focus and were complementary (Atherton et al., 2015). Other systematic reviews showed that reported agreement between CTCAE and PRO ratings was poor to moderate in most trials (Atkinson et al., 2016). They provided evidence that PROs provided unique, valuable information that can complement CTCAE ratings, avoiding loss of AEs information because of a long interval between visits (Atkinson et al., 2016). The PRO-CTCAE included a rigorous method for capturing patient self-reports of symptomatic AEs in cancer clinical trials (Hagelstein et al., 2016) but has not been used

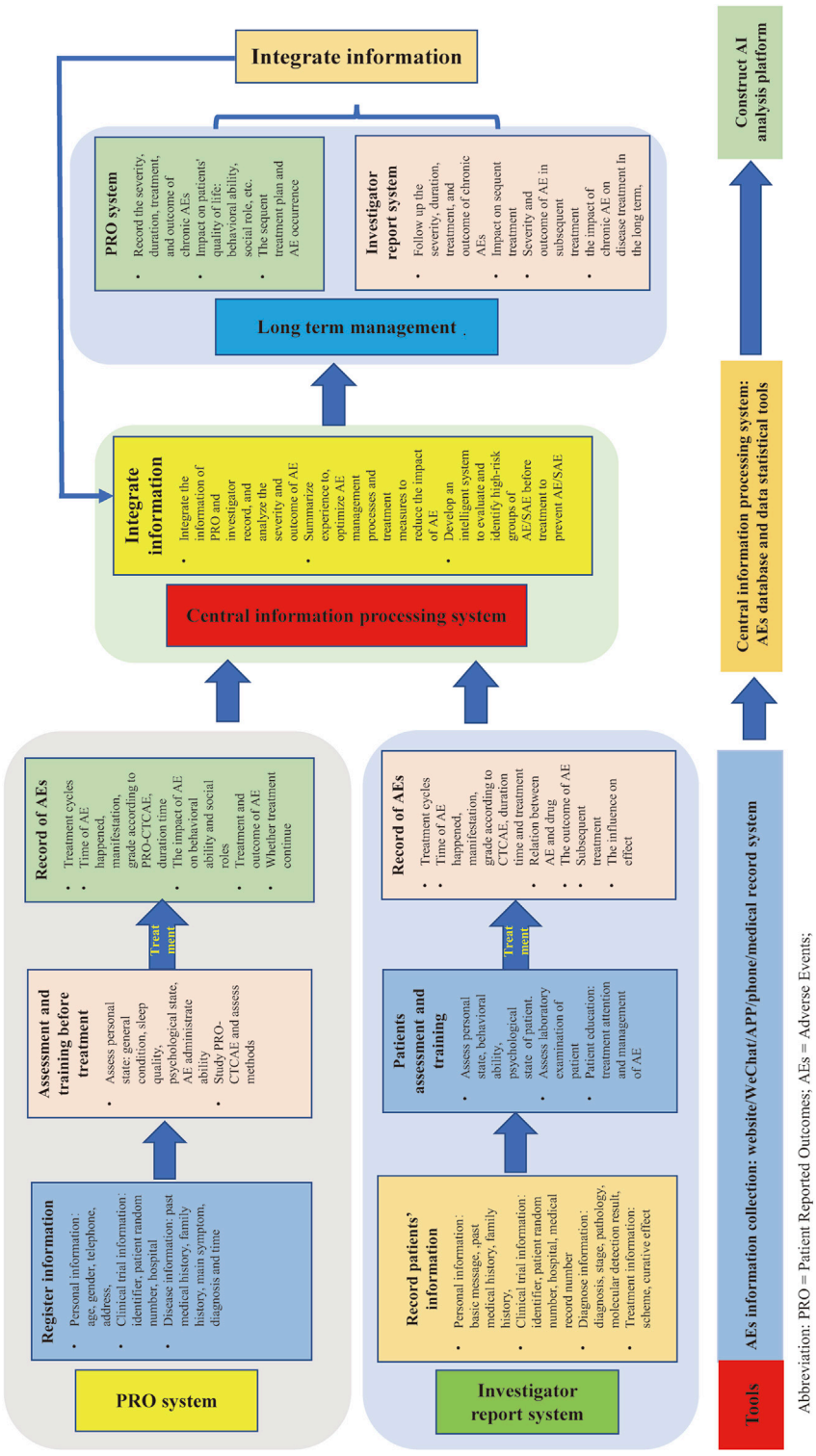

FIGURE 6 | PRO and investigator system AEs comprehensive reporting process.

worldwide. The effective combination of the PRO-CTCAE and clinician-reported CTCAE may be better for the management of AEs, especially SAEs, in cancer patients.

SAEs reports need more improvement. For example, improving the construction of SAEs reporting systems in electronic information platforms, establishing precise process

and data collection methods, strengthening the training of medical staff, enhancing the safety ability assessment of patients via patient education, and improving the awareness and attention of SAEs have been reported. The authors believe that co-report of AEs/SAEs via PRO and researchers in clinical trials should be adopted in the future (**Figure 6**).

There were some shortcomings in this study. First, this was a retrospective study, and there may be omissions in data collection and selection bias. Second, the identification criteria for SAEs may vary because of the diverse designs of clinical trials and different judgment criteria of investigators. Third, bias existed in the data collection because the descriptions of SAEs in the publications were inconsistently attributed to the journal-specific publication requirements. Finally, this study's included publications were all published clinical trials, and unpublished clinical trials, such as clinical trials with negative research results, were excluded. The reporting methods for SAEs have gradually improved as people pay increasing attention to SAEs. Independent reporting of SAEs by patients and researchers may better guide clinical practice and drug development in the future.

CONCLUSION

In conclusion, our findings showed that the RP of SAEs increased and aroused more researchers' attention over time. However, more efforts should be made to improve the RP of SAEs and the quality of SAEs reporting. The patterns and outcomes of SAEs should be reported in detail and given more attention to better guide drug application by clinicians in the real world. In addition, independent reporting of SAEs by patients and researchers should be encouraged.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.754858/full#supplementary-material

REFERENCES

André, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T., Topham, C., et al. (2009). Improved Overall Survival with Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment in Stage II or III colon Cancer in the MOSAIC Trial. *J. Clin. Oncol.* 27 (19), 3109–3116. doi:10.1200/jco.2008.20.6771

Atherton, P. J., Watkins-Bruner, D. W., Gotay, C., Moinpour, C. M., Satele, D. V., Winter, K. A., et al. (2015). The Complementary Nature of Patient-Reported Outcomes and Adverse Event Reporting in Cooperative Group Oncology Clinical Trials: a Pooled Analysis (NCCTG N0591). *J. Pain Symptom Manage.* 50 (4), 470–e9. e479. doi:10.1016/j.jpainsymman.2015.04.016

Atkinson, T. M., Ryan, S. J., Bennett, A. V., Stover, A. M., Saracino, R. M., Rogak, L. J., et al. (2016). The Association between Clinician-Based Common Terminology Criteria for Adverse Events (CTCAE) and Patient-Reported Outcomes (PRO): a Systematic Review. *Support Care Cancer* 24 (8), 3669–3676. doi:10.1007/s00520-016-3297-9

Bennouna, J., Sastre, J., Arnold, D., sterlund, P., Greil, R., Van Cutsem, E., et al. (2013). Continuation of Bevacizumab After First Progression in Metastatic Colorectal Cancer (ML18147): A Randomised Phase 3 Trial. *Lancet Oncol.* 14, 29–37. doi:10.1016/S1470-2045(12)70477-1

Bekaii-Saab, T. S., Ou, F. S., Ahn, D. H., Boland, P. M., Ciombor, K. K., Heying, E. N., et al. (2019). Regorafenib Dose-Optimisation in Patients with Refractory Metastatic Colorectal Cancer (ReDOS): a Randomised, Multicentre, Open-Label, Phase 2 Study. *Lancet Oncol.* 20 (8), 1070–1082. doi:10.1016/s1470-2045(19)30272-4

Bhattacharyya, A., Gallo, P., Crisp, A., Lavange, L., Molenberghs, G., Pétavy, F., et al. (2018). The Changing Landscape of Data Monitoring Committees-Perspectives from Regulators, Members, and Sponsors. *Biom. J.* 61 (5), 1232–1241. doi:10.1002/bimj.201700307

Bouché, O., Ben Abdelghani, M., Labourey, J. L., Triby, S., Bensadoun, R. J., Jouary, T., et al. (2019). Management of Skin Toxicities during Panitumumab Treatment in Metastatic Colorectal Cancer. *World J. Gastroenterol.* 25 (29), 4007–4018. doi:10.3748/wjg.v25.i29.4007

Cascinu, S., Rosati, G., Nasti, G., Lonardi, S., Zaniboni, A., Marchetti, P., et al. (2017). Treatment Sequence with Either Irinotecan/Cetuximab Followed By FOLFOX-4 or the Reverse Strategy in Metastatic Colorectal Cancer Patients Progressing After First-Line FOLFIRI/Bevacizumab: An Italian Group For the Study of Gastrointestinal Cancer Phase III, Randomised Trial Comparing Two Sequences of Therapy in Colorectal Metastatic Patients. *Eur. J. Cancer* 83, 106e115. doi:10.1016/j.ejca.2017.06.029

Chen, H. X., Mooney, M., Boron, M., Vena, D., Mosby, K., Grochow, L., et al. (2006). Phase II Multicenter Trial of Bevacizumab Plus Fluorouracil and Leucovorin in Patients with Advanced Refractory Colorectal Cancer: an NCI Treatment Referral Center Trial TRC-0301. *J. Clin. Oncol.* 24 (21), 3354–3360. doi:10.1200/jco.2005.05.1573

Chung, A. E., Shoenbill, K., Mitchell, S. A., Dueck, A. C., Schrag, D., Bruner, D. W., et al. (2019). Patient Free Text Reporting of Symptomatic Adverse Events in Cancer Clinical Research Using the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J. Am. Med. Inform. Assoc.* 26 (4), 276–285. doi:10.1093/jamia/ocy169

Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (2017). *Common Terminology Criteria for Adverse Events (CTCAE) v5.0*. U.S. Department of Health and Human Services National Institutes of Health National Cancer Institute. Available at https://www.meddra.org/ (Cited November 27, 2017).

Crépin, S., Villeneuve, C., and Merle, L. (2016). Quality of Serious Adverse Events Reporting to Academic Sponsors of Clinical Trials: Far from Optimal. *Pharmacoepidemiol. Drug Saf.* 25 (6), 719–724. doi:10.1002/pds.3982

Cunningham, D., Lang, I., Marcuello, E., Lorusso, V., Ocvirk, J., Shin, D.B., et al. (2013). Bevacizumab Plus Capecitabine Versus Capecitabine Alone in Elderly Patients with Previously Untreated Metastatic Colorectal Cancer (AVEX): An Open-Label, Randomised Phase 3 Trial. *Lancet Oncol.* 14, 1077–1085. doi:10.1016/S1470-2045(13)70154-2

De Gramont, A., Van Cutsem, E., Schmoll, H.-J., Tabernero, J., Clarke, S., Moore, M.J., et al. (2012). Bevacizumab Plus Oxaliplatin-Based Chemotherapy as Adjuvant Treatment For Colon Cancer (AVANT): A Phase 3 Randomised Controlled Trial. *Lancet Oncol.* 13 (12), 1225–1233. doi:10.1016/s1470-2045(12)70509-0

Douillard, J.-Y., Siena, S., Cassidy, J., Tabernero, J., Burkes, R., Barugel, M., et al. (2010). Randomized, Phase III Trial of Panitumumab with Infusional Fluorouracil, Leucovorin, And Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone as First-Line Treatment in Patients with Previously Untreated Metastatic Colorectal Cancer: The PRIME Study. *J. Clin. Oncol.* 28 (31), 4697–4705. doi:10.1200/jco.2009.27.4860

Eduardo, D.-R., Auxiliadora, G.-E., Bartomeu, M., Javier, S., Albert, A., Manuel, V., et al. (2012). First-Line XELOX Plus Bevacizumab Followed By XELOX Plus Bevacizumab or Single-Agent Bevacizumab As Maintenance Therapy in Patients with Metastatic Colorectal Cancer: The Phase III MACRO TTD Study. *Oncologist* 17, 15–25. doi:10.1634/theoncologist.2011-0249

Fields, A.L.A., Keller, A., Schwartzberg, L., Bernard, S., Kardinal, C., Cohen, A., et al. (2009). Adjuvant Therapy with the Monoclonal Antibody Edrecolomab Plus Fluorouracil-Based Therapy Does Not Improve Overall Survival of Patients with Stage III Colon Cancer. *J. Clin. Oncol.* 27 (12), 1941–1947. doi:10.1200/jco.2008.18.5710

Fitzmaurice, C., Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., et al. (2017). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life-Years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 3 (4), 524–548. doi:10.1001/jamaoncol.2016.5688

Grothey, A., Van Cutsem, E., Sobrero, A., Siena, S., Falcone, A., Ychou, M., et al. (2013). Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer (CORRECT): an International, Multicentre, Randomised, Placebo-Controlled, Phase 3 Trial. *Lancet* 381 (26), 303–312. doi:10.1016/S0140-6736(12)61900-X

Group, Q. C., Gray, R., Barnwell, J., McConkey, C., Hills, R. K., Williams, N. S., et al. (2007). Adjuvant Chemotherapy versus Observation in Patients with Colorectal Cancer: a Randomised Study. *Lancet* 370 (9604), 2020–2029. doi:10.1016/s0140-6736(07)61866-2

Guan, Z.Z., Xu, J.M., Luo, R.C., Feng, F.Y., Wang, L.-W., Shen, L., et al. (2011). Efficacy And Safety of Bevacizumab Plus Chemotherapy in Chinese Patients with Metastatic Colorectal Cancer: A Randomized Phase III ARTIST Trial. *Chin. J. Cancer*. 30 (10), 682–689. doi:10.5732/cjc.011.10188

Hagelstein, V., Ortland, I., Wilmer, A., Mitchell, S. A., and Jaehde, U. (2016). Validation of the German Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™). *Ann. Oncol.* 27 (12), 2294–2299. doi:10.1093/annonc/mdw422

Hecht, J.R., Mitchell, E., Chidiac, T., Scroggin, C., Hagenstad, C., Spigel, D., et al. (2009). A Randomized Phase IIIB Trial of Chemotherapy, Bevacizumab, And Panitumumab Compared with Chemotherapy And Bevacizumab Alone For Metastatic Colorectal Cancer. *J. Clin. Oncol.* 27 (5), 672–680. doi:10.1200/jco.2008.19.8135

Hecht, J.R., Trarbach, T., Hainsworth, J.D., Major, P., Jäger, E., Wolff, R.A., et al. (2011). Randomized, Placebocontrolled, Phase III Study of First-Line Oxaliplatin-Based Chemotherapy Plus PTK787/ZK 222584, An Oral Vascular Endothelial Growth Factor Receptor Inhibitor, in Patients with Metastatic Colorectal Adenocarcinoma. *J. Clin. Oncol.* 29 (15), 1997–2003. doi:10.1200/jco.2010.29.4496

Hoff, P.M., Hochhaus, A., Pestalozzi, B.C., Tebbutt, N.C., Li, J., Kim, T.W., et al. (2012). Cediranib Plus FOLFOX/CAPOX Versus Placebo Plus FOLFOX/CAPOX in Patients with Previously Untreated Metastatic Colorectal Cancer: A Randomized, Double-Blind, Phase III Study (HORIZON II). *J. Clin. Oncol.* 30 (29), 3596–3603. doi:10.1200/jco.2012.42.6031

Hong, Y. S., Lee, J., Kim, K. P., Lee, J. L., Park, Y. S., Park, J. O., et al. (2012). Multicenter Phase II Study of Second-Line Bevacizumab Plus Doublet Combination Chemotherapy in Patients with Metastatic Colorectal Cancer Progressed after Upfront Bevacizumab Plus Doublet Combination Chemotherapy. *Invest. New Drugs* 31 (1), 183–191. doi:10.1007/s10637-012-9853-3

Horita, Y., Yamada, Y., Kato, K., Hirashima, Y., Akiyoshi, K., Nagashima, K., et al. (2011). Phase II Clinical Trial of Second-Line FOLFIRI Plus Bevacizumab for Patients with Metastatic Colorectal Cancer: AVASIRI Trial. *Int. J. Clin. Oncol.* 17 (6), 604–609. doi:10.1007/s10147-011-0331-2

Iveson, T. J., Kerr, R. S., Saunders, M. P., Cassidy, J., Hollander, N. H., Tabernero, J., et al. (2018). 3 versus 6 Months of Adjuvant Oxaliplatin-Fluoropyrimidine Combination Therapy for Colorectal Cancer (SCOT): an International, Randomised, Phase 3, Non-inferiority Trial. *Lancet Oncol.* 19 (4), 562–578. doi:10.1016/s1470-2045(18)30093-7

Kerr, R.S., Love, S., Segelov, E., Johnstone, E.C., Falcon, B., Hewett, P., et al. (2016). Adjuvant Capecitabine Plus Bevacizumab Versus Capecitabine Alone in Patients with Colorectal Cancer (QUASAR 2): An Open-Label, Randomised Phase 3 Trial. *Lancet Oncol.* 17, 1543–1557. doi:10.1016/S1470-2045(16)30172-3

Köhne, C.-H., Bedenne, L., Carrato, A., Bouché, O., Popov, I., Gaspà, L., et al. (2013). A Randomised Phase III Intergroup Trial Comparing High-Dose Infusional 5-Fluorouracil with or Without Folinic Acid with Standard Bolus 5-Fluorouracil/Folinic Acid in the Adjuvant Treatment of Stage III Colon Cancer: The Pan-European Trial in Adjuvant Colon Cancer 2 Study. *Eur. J. Cancer* 49 (8), 1868–1875. doi:10.1016/j.ejca.2013.01.030

Köhne, C.H., Van Cutsem, E., Wils, J., Bokemeyer, C., El-Serafi, M., Lutz, M.P., et al. (2005). Phase III Study of Weekly High-Dose Infusional Fluorouracil Plus Folinic Acid with or Without Irinotecan in Patients with Metastatic Colorectal Cancer: European Organisation For Research And Treatment of Cancer Gastrointestinal Group Study 40986. *J. Clin. Oncol.* 23 (22), 4856–4865. doi:10.1200/jco.2005.05.546

Kuusisto, H., Virkki, M., Wuolijoki, E., and Keränen, T. (2011). Hospital Training Program Increases Awareness of Good Clinical Practice (GCP). *Contemp. Clin. Trials* 32 (3), 339–341. doi:10.1016/j.cct.2011.01.011

Lencioni, A., Hutchins, L., Annis, S., Chen, W., Ermisoglu, E., Feng, Z., et al. (2015). An Adverse Event Capture and Management System for Cancer Studies. *BMC Bioinformatics* 16 Suppl 13 (S13), S6. doi:10.1186/1471-2105-16-s13-s6

Li, J., Qin, S., Xu, R., Yau, T. C., Ma, B., Pan, H., et al. (2015). Regorafenib Plus Best Supportive Care versus Placebo Plus Best Supportive Care in Asian Patients with Previously Treated Metastatic Colorectal Cancer (CONCUR): a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol.* 16 (6), 619–629. doi:10.1016/s1470-2045(15)70156-7

Li, J., Qin, S., Xu, R. H., Shen, L., Xu, J., Bai, Y., et al. (2018). Effect of Fruquintinib vs Placebo on Overall Survival in Patients with Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. *JAMA* 319 (24), 2486–2496. doi:10.1001/jama.2018.7855

Li, J., Xu, R., Qin, S., Liu, T., Pan, H., Xu, J., et al. (2018). Aflibercept Plus FOLFIRI in Asian Patients with Pretreated Metastatic Colorectal Cancer: a Randomized Phase III Study. *Future Oncol.* 14 (20), 2031–2044. doi:10.2217/fon-2017-0669

Li, N., Huang, H. Y., Wu, D. W., Yang, Z. M., Wang, J., Wang, J. S., et al. (2019). Changes in Clinical Trials of Cancer Drugs in mainland China over the Decade 2009-18: a Systematic Review. *Lancet Oncol.* 20 (11), e619–e626. doi:10.1016/s1470-2045(19)30491-7

Lineberry, N., Berlin, J. A., Mansi, B., Glasser, S., Berkwits, M., Klem, C., et al. (2016). Recommendations to Improve Adverse Event Reporting in Clinical Trial Publications: a Joint Pharmaceutical Industry/journal Editor Perspective. *BMJ* 355, i5078. doi:10.1136/bmj.i5078

Lonardi, S., Sobrero, A., Rosati, G., Di Bartolomeo, M., Ronzoni, M., Aprile, G., et al. (2016). Phase III Trial Comparing 3–6 Months of Adjuvant FOLFOX4/XELOX in Stage II–III Colon Cancer: Safety And Compliance in the TOSCA Trial. *Ann. Oncol.* 27 (11), 2074–2081. doi:10.1093/annonc/mdw404

London, J. W., Smalley, K. J., Conner, K., and Smith, J. B. (2009). The Automation of Clinical Trial Serious Adverse Event Reporting Workflow. *Clin. Trials* 6 (5), 446–454. doi:10.1177/1740774509344778

Loupakis, F., Cremolini, C., Masi, G., Lonardi, S., Zagonel, V., Salvatore, L., et al. (2014). Initial Therapy with FOLFOXIRI And Bevacizumab For Metastatic Colorectal Cancer. *N. Engl. J. Med.* 371 (23), 1609–1618. doi:10.1056/NEJMoa1403108

Lynch, T. J., Jr, Kim, E. S., Eaby, B., Garey, J., West, D. P., and Lacouture, M. E. (2007). Epidermal Growth Factor Receptor Inhibitor-Associated Cutaneous Toxicities: an Evolving Paradigm in Clinical Management. *Oncologist* 12 (5), 610–621. doi:10.1634/theoncologist.12-5-610

Masi, G., Salvatore, L., Boni, L., Loupakis, F., Cremolini, C., Fornaro, L., et al. (2015). Continuation or Reintroduction of Bevacizumab Beyond Progression To First-Line Therapy in Metastatic Colorectal Cancer: Final Results of the Randomized BEBYP Trial. *Ann. Oncol.* 26, 724–730. doi:10.1093/annonc/mdv012

Moore, T. J., Cohen, M. R., and Furberg, C. D. (2007). Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005. *Arch. Intern. Med.* 167 (16), 1752–1759. doi:10.1001/archinte.167.16.1752

Munemoto, Y., Kanda, M., Oba, K., Kim, H. M., Takemoto, H., Denda, T., et al. (2018). A Phase II Trial to Evaluate the Efficacy of Panitumumab Combined with Fluorouracil-Based Chemotherapy for Metastatic Colorectal Cancer: the PF Trial. *Cancer Chemother. Pharmacol.* 81 (5), 829–838. doi:10.1007/s00280-018-3556-1

Nakayama, G., Uehara, K., Ishigure, K., Yokoyama, H., Ishiyama, A., Eguchi, T., et al. (2012). The Efficacy and Safety of Bevacizumab beyond First Progression in Patients Treated with First-Line mFOLFOX6 Followed by Second-Line FOLFIRI in Advanced Colorectal Cancer: a Multicenter, Single-Arm, Phase II Trial (CCOG-0801). *Cancer Chemother. Pharmacol.* 70 (4), 575–581. doi:10.1007/s00280-012-1948-1

Nishi, T., Hamamoto, Y., Nagase, M., Denda, T., Yamaguchi, K., Amagai, K., et al. (2016). Phase II Trial of Panitumumab with Irinotecan as Salvage Therapy for Patients with Advanced or Recurrent Colorectal Cancer (TOPIC Study). *Oncol. Lett.* 11 (6), 4049–4054. doi:10.3892/ol.2016.4532

Papadimitriou, C.A., Papakostas, P., Karina, M., Malettou, L., Dimopoulos, M.A., Pentheroudakis, G., et al. (2011). A Randomized Phase III Trial of Adjuvant Chemotherapy with Irinotecan, Leucovorin And Fluorouracil Versus Leucovorin And Fluorouracil For Stage II And III Colon Cancer: A Hellenic Cooperative Oncology Group Study. *BMC Medicine* 9 (1). doi:10.1186/1741-7015-9-10

Pecoraro, F., and Luzi, D. (2011). Serious Adverse Event Reporting in a Medical Device Information System. *Stud. Health Technol. Inform.* 169, 834–838. doi:10.3233/978-1-60750-806-9-834

Peeters, M., Price, T.J., Cervantes, A., Sobrero, A.F., Ducreux, M., Hotko, Y., et al. (2010). Randomized Phase III Study of Panitumumab with Fluorouracil, Leucovorin, And Irinotecan (FOLFIRI) Compared with FOLFIRI Alone as Second-Line Treatment in Patients with Metastatic Colorectal Cancer. *J Clin. Oncol.* 28 (31), 4706–4713. doi:10.1200/jco.2009.27.6055

Péron, J., Maillet, D., Gan, H. K., Chen, E. X., and You, B. (2013). Adherence to CONSORT Adverse Event Reporting Guidelines in Randomized Clinical Trials Evaluating Systemic Cancer Therapy: a Systematic Review. *J. Clin. Oncol.* 31 (31), 3957–3963. doi:10.1200/jco.2013.49.3981

Popov, I., Carrato, A., Sobrero, A., Vincent, M., Kerr, D., Labianca, R., et al. (2008). Raltitrexed (Tomudex®) Versus Standard Leucovorin-Modulated Bolus 5-Fluorouracil: Results From the Randomised Phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1). *Eur. J. Cancer.* 44 (15), 2204–2211. doi:10.1016/j.ejca.2008.07.002

Porschen, R., Arkenau, H.-T., Kubicka, S., Greil, R., Seufferlein, T., Freier, W., et al. (2007). Phase III Study of Capecitabine Plus Oxaliplatin Compared with Fluorouracil And Leucovorin Plus Oxaliplatin in Metastatic Colorectal Cancer: A Final Report of the AIO Colorectal Study Group. *J. Clin. Oncol.* 25 (27), 4217–4223. doi:10.1200/jco.2006.09.2684

Qin, S., Li, J., Wang, L., Xu, J., Cheng, Y., Bai, Y., et al. (2018). Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) versus FOLFOX-4 in Patients with RAS Wild-type Metastatic Colorectal Cancer: the Open-Label, Randomized, Phase III TAILOR Trial. *J. Clin. Oncol.* 36 (30), 3031–3039. doi:10.1200/jco.201810.1200/JCO.2018.78.3183

Saini, A., Norman, A.R., Cunningham, D., Chau, I., Hill, M., Tait, D., et al. (2003). Twelve Weeks of Protracted Venous Infusion of Fluorouracil (5-FU) Is As Effective As 6 Months of Bolus 5-FU And Folinic Acid As Adjuvant Treatment in Colorectal Cancer. *Brit. J. Cancer.* 88 (12), 1859–1865. doi:10.1038/sj.bjc.6600995

Saltz, L. B., Clarke, S., Díaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R., et al. (2008). Bevacizumab in Combination with Oxaliplatin-Based Chemotherapy as First-Line Therapy in Metastatic Colorectal Cancer: a Randomized Phase III Study. *J. Clin. Oncol.* 26 (12), 2013–2019. doi:10.1200/jco.2007.14.9930

Sartor, O. (2017). Adverse Event Reporting in Clinical Trials: Time to Include Duration as Well as Severity. *Oncologist* 23 (1), 1. doi:10.1634/theoncologist.2017-0437

Scharf, O., and Colevas, A. D. (2006). Adverse Event Reporting in Publications Compared with Sponsor Database for Cancer Clinical Trials. *J. Clin. Oncol.* 24 (24), 3933–3938. doi:10.1200/jco.2005.05.3959

Schmoll, H.-J., Cartwright, T., Tabernero, J., Nowacki, M.P., Figer, A., Maroun, J., et al. (2007). Phase III Trial of Capecitabine Plus Oxaliplatin As Adjuvant Therapy For Stage III Colon Cancer: A Planned Safety Analysis in 1,864 Patients. *J. Clin. Oncol.* 26 (1), 102–109. doi:10.1200/jco.2006.08.1075

Schmoll, H.-J., Cunningham, D., Sobrero, A., Karapetis, C.S., Rougier, P., Koski, S.L., et al. (2012). Cediranib with Mfolfox6 Versus Bevacizumab with Mfolfox6 as First-Line Treatment For Patients with Advanced Colorectal Cancer: A Doubleblind, Randomized Phase III Study (HORIZON III). *J. Clin. Oncol.* 30, 3588–3595. doi:10.1200/JCO.2012.42.5355

Shanley, T. P., Calvin-Naylor, N. A., Divecha, R., Wartak, M. M., Blackwell, K., Davis, J. M., et al. (2017). Enhancing Clinical Research Professionals' Training and Qualifications (ECRPTQ): Recommendations for Good Clinical Practice (GCP) Training for Investigators and Study Coordinators. *J. Clin. Transl. Sci.* 1 (1), 8–15. doi:10.1017/cts.2016.1

Sivendran, S., Latif, A., Mcbride, R. B., Stensland, K. D., Wisnivesky, J., Haines, L., et al. (2014). Adverse Event Reporting in Cancer Clinical Trial Publications. *J. Clin. Oncol.* 32 (2), 83–89. doi:10.1200/jco.2013.52.2219

Sobrero, A.F., Maurel, J., Fehrenbacher, L., Scheithauer, W., Abubakr, Y.A., Lutz, M.P., et al. (2008). EPIC: Phase III Trial of Cetuximab Plus Irinotecan After Fluoropyrimidine And Oxaliplatin Failure in Patients with Metastatic Colorectal Cancer. *J. Clin. Oncol.* 26 (14), 2311–2319. doi:10.1200/jco.2007.13.1193

Soda, H., Maeda, H., Hasegawa, J., Takahashi, T., Hazama, S., Fukunaga, M., et al. (2015). Multicenter Phase II Study of FOLFOX or Biweekly XELOX and Erbitux (Cetuximab) as First-Line Therapy in Patients with Wild-type KRAS/BRAF Metastatic Colorectal Cancer: The FLEET Study. *BMC Cancer* 15 (1), 695. doi:10.1186/s12885-015-1685-z

Soeda, H., Shimodaira, H., Gamoh, M., Ando, H., Isobe, H., Suto, T., et al. (2014). Phase II Trial of Cetuximab Plus Irinotecan for Oxaliplatin- and Irinotecan-Based Chemotherapy-Refractory Patients with Advanced And/or Metastatic Colorectal Cancer: Evaluation of Efficacy and Safety Based on KRAS Mutation Status (T-Core0801). *Oncology* 87 (1), 7–20. doi:10.1159/000360989

Sonawane, K. B., Cheng, N., and Hansen, R. A. (2018). Serious Adverse Drug Events Reported to the FDA: Analysis of the FDA Adverse Event Reporting System 2006-2014 Database. *J. Manag. Care Spec. Pharm.* 24 (7), 682–690. doi:10.18553/jmcp.2018.24.7.682

Song, S. Y., and Kim, E. (2020). The Clinical Trial Transparency in Oncology Significantly Increased over the Recent Years. *J. Clin. Epidemiol.* 119, 100–108. doi:10.1016/j.jclinepi.2019.11.018

Tournigand, C., André, T., Achille, E., Lledo, G., Flesh, M., Mery-Mignard, D., et al. (2004). FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: a Randomized GERCOR Study. *J. Clin. Oncol.* 22 (2), 229–237. doi:10.1200/jco.2004.05.113

Van Cutsem, E., Bajetta, E., Valle, J., Köhne, C.-H., Randolph Hecht, J., Moore, M., et al. (2011). Randomized, Placebo-Controlled, Phase III Study of Oxaliplatin, Fluorouracil, And Leucovorin with or Without PTK787/ZK 222584 in Patients with Previously Treated Metastatic Colorectal Adenocarcinoma. *J. Clin. Oncol.* 29 (15), 2004–2010. doi:10.1200/jco.2010.29.5436

Van Cutsem, E., Köhne, C. H., Hitre, E., Zaluski, J., Chang Chien, C. R., Makhson, A., et al. (2009). Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. *N. Engl. J. Med.* 360, 1408–1417. doi:10.1056/NEJMoa0805019

Van Cutsem, E., Yoshino, T., Lenz, H.J., Lonardi, S., Falcone, A., Limo´N, M.L., et al. (2018). Nintedanib For the Treatment of Patients with Refactory Metastatic Colorectal Cancer (LUME-Colon 1): A Phase III, International, Randomized, Placebo-Controlled Study. *Ann. Oncol.* 29, 1955–1963. doi:10.1093/annonc/mdy241

Van Hazel, G.A., Heinemann, V., Sharma, N.K., Findlay, M.P.N., Ricke, J., Peeters, M., et al. (2016). SIRFLOX: Randomized Phase III Trial Comparing First-Line Mfolfox6 (Plus or Minus Bevacizumab) Versus Mfolfox6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients with Metastatic Colorectal Cancer. *J. Clin. Oncol.* 34 (15), 1723–1731. doi:10.1200/jco.2015.66.1181

Wallace, S., Myles, P. S., Zeps, N., and Zalcberg, J. R. (2016). Serious Adverse Event Reporting in Investigator-Initiated Clinical Trials. *Med. J. Aust.* 204 (6), 231–233. doi:10.5694/mja15.01007

Wang, M. (2017). Clinical Trials and Drug Approvals Continue to Accelerate in China. *Lancet Oncol.* 18 (7), 855. doi:10.1016/s1470-2045(17)30406-0

Wasan, H.S., Gibbs, P., Sharma, N.K., Taieb, J., Heinemann, V., Ricke, J., et al. (2017). First-Line Selective Internal Radiotherapy Plus Chemotherapy Versus Chemotherapy Alone in Patients with Liver Metastases From Colorectal Cancer (FOXFIRE, SIRFLOX, And FOXFIRE-Global): A Combined Analysis of Three Multicentre, Randomised, Phase 3 Trials. *Lancet Oncol.* 18, 1159–1171. doi:10.1016/S1470-2045(17)30457-6

Xu, J., Kim, T.W., Shen, L., Sriuranpong, V., Pan, H., Xu, R., et al. (2018). Results of a Randomized, Double-Blind, Placebocontrolled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients with Previously Treated Metastatic Colorectal Cancer: The TERRA Study. *J. Clin. Oncol.* 36 (4), 350-358. doi:10.1200/jco.2017

Xu, RH., Muro, K., Morita, S., Iwasa, S., Han, S.W., Wang, W., et al. (2018). Modified XELIRI (Capecitabine Plus Irinotecan) Versus FOLFIRI (Leucovorin,

Fluorouracil, And Irinotecan), Both Either with or Without Bevacizumab, As Second-Line Therapy For Metastatic Colorectal Cancer (AXEPT): A Multicentre, Open-Label, Randomised, Noninferiority, Phase 3 Trial. *Lancet Oncol.* 19 (5), 660–671. doi:10.1016/s1470-2045(18)30140-2

Ychou, M., Hohenberger, W., Thezenas, S., Navarro, M., Maurel, J., Bokemeyer, C., et al. (2009). A Randomized Phase III Study Comparing Adjuvant 5-Fluorouracil/Folinic Acid with FOLFIRI in Patientsfoll Owing Complete Resection of Liver Metastases From Colorectal Cancer. *Ann. Oncol.* 20, 1964–1970. doi:10.1093/annonc/mdp236

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Deprescribing Antipsychotics Based on Real-World Evidence to Inform Clinical Practice: Safety Considerations in Managing Older Adults with Dementia

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Background: Antipsychotics are commonly used in dementia patients but have potential risks that often outweigh clinical benefits. Limited studies have assessed the healthcare utilization and medical costs associated with antipsychotic use, especially those focused on cumulative days of use.

Objectives: To examine clinical and economic burdens associated with different cumulative days of antipsychotic use in older adults with dementia in the United States.

Methods: This study used Medicare Current Beneficiary Survey (2015–2017). Older (≥65 years) Medicare beneficiaries with dementia, without concurrent schizophrenia, bipolar disorder, Huntingon's disease, or Tourette's syndrome were included. Antipsychotic use was measured using Medicare Part D prescription events. Healthcare utilization was measured as inpatient services, outpatient services, and emergency room (ER) visits. Total medical costs were classified as Medicare and out-of-pocket costs. The logistic regression, negative binomial regression, and generalized linear model with a log link and gamma distribution were used to examine factors, healthcare utilization, and medical costs. Survey sampling weights were applied to generate national estimates.

Results: Among older adults with dementia, 13.18% used antipsychotics. Factors associated with antipsychotic use were being Hispanic (OR: 2.90; 95% CI: 1.45, 5.78), widowed (OR: 3.52; 95% CI: 1.46, 8.48), and single (OR: 3.25; 95% CI: 1.53, 6.87). Compared to non-users, antipsychotic use was associated with higher inpatient visits (IRR: 2.11; 95% CI 1.53, 2.90), ER visits (IRR: 1.61; 95% CI: 1.21, 2.13), total costs (β: 0.53; 95% CI: 0.36, 0.71), Medicare costs (β: 0.49; 95% CI 0.26, 0.72), and out-of-pocket costs (β: 0.66; 95% CI: 0.35, 0.97). With the increase in cumulative days of antipsychotic use, the magnitude of clinical and economic burdens was decreased.

Conclusion: The significant clinical and economic burdens associated with antipsychotic use, especially with short-term use, provide real-world evidence to inform clinical practice on deprescribing antipsychotics among community-dwelling geriatric dementia patients.

Keywords: dementia, antipsychotics, deprescribing, real-world evidence, older adults

INTRODUCTION

Dementia is a syndrome characterized by progressive cognitive function deterioration with various etiology (van der Flier and Scheltens, 2005). Alzheimer's disease is the most common type of dementia, which is estimated to affect more than five million older adults aged 65 years and over (Alzheimer's Association, 2020). The public health impact of dementia is significant. Individuals with dementia utilized hospital and emergency room (ER) services two times more frequently than those without dementia (Alzheimer's Association, 2020). The total healthcare costs incurred by individuals with Alzheimer's disease are estimated to be more than $300 billion and the indirect costs (e.g., care provided by unpaid caregivers) are estimated to value more than $200 billion in the United States (Alzheimer's Association, 2020).

One of the most stressful and costly aspects of dementia care involves the management of behavioral and psychological symptoms of dementia (BPSD) (Kales et al., 2015). BPSD encompasses a range of symptoms caused by disturbances in the individual's mood, behavior, thoughts, and perception; symptoms of BPSD include agitation, psychosis, and aggression (Kales et al., 2015). It is highly prevalent and is estimated to affect up to 80% of individuals with dementia (Kirkham et al., 2017). Non-pharmacological treatment is recommended as first-line for its management to reduce the risks of adverse events with pharmacological therapies (Reus et al., 2016; Kirkham et al., 2017). Family caregiver interventions, environmental strategies, and patient-oriented approaches are all potential non-pharmacological approaches that can be attempted initially to manage BPSD (Kales et al., 2015). However, these strategies might not always be effective and appropriate when BPSD symptoms are severe, dangerous, and cause significant patient distress (Reus et al., 2016).

When non-pharmacological therapy fails or is not appropriate alone for BPSD symptoms, clinical practice guidelines suggest that pharmacological therapy might be used (Reus et al., 2016). Among various therapeutic options, antipsychotics are the most extensively studied and commonly used agents (Liperoti et al., 2008; Kales et al., 2015; Kirkham et al., 2017). Antipsychotic agents block D2 receptors in various cerebral regions to modulate the effects of dopamine and, subsequently, BPSD symptoms (Liperoti et al., 2008).

The use of antipsychotics in older adults with dementia requires a careful assessment of clinical benefit for BPSD symptoms against their potential risks (Reus et al., 2016). Serious adverse events, such as mortality and cerebrovascular accidents, are found to be associated with antipsychotic use in older adults (Maust et al., 2015; Tampi et al., 2016; Zhai et al., 2016). The U.S. Food and Drug Administration has issued a black box warning advising the increased mortality risk associated with antipsychotic use in patients with dementia (Kim et al., 2011). Some medical societies have advised the judicious use of antipsychotics in treating BPSD symptoms in dementia, including American Geriatrics Society through its Beers Criteria, American Board of Internal Medicine through their Choosing Wisely campaign, and the American Psychiatric Association (Reus et al., 2016; American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). However, the use of antipsychotics remain common in dementia patients (Kirkham et al., 2017).

Limited studies have assessed the healthcare utilization and medical costs associated with antipsychotic use, especially those focused on cumulative days of use. Evidence on whether antipsychotic use among older adults with dementia was associated with an increase in acute hospital admissions is conflicting. (Raivio et al., 2007; Rochon et al., 2008). Older adults with Alzheimer's disease were more likely to visit the emergency department due to psychotropic-related adverse drug effects, with antipsychotic agents commonly implicated in these visits (Sepassi and Watanabe, 2019). Total healthcare costs were significantly greater among patients with Alzheimer's disease who used second-generation antipsychotics (Rosenheck et al., 2007). The clinical utility of existing studies is limited as most did not examine cumulative days of antipsychotic use and did not differentiate between different types of healthcare utilization and medical costs. To fill the gap in the literature, the objectives of this study were: 1) to evaluate factors associated with antipsychotic use, 2) to examine healthcare utilization associated with cumulative days of antipsychotic use, and 3) to assess medical costs of cumulative days of antipsychotic use in older adults with dementia.

METHODS

Data Source

This study used the Medicare Current Beneficiary Survey (MCBS) from 2015 to 2017. The MCBS is a nationally representative survey of Medicare beneficiaries conducted by the Centers for Medicare and Medicaid Services in the United States (Medicare Current Beneficiary Survey (MCBS), 2019). Through linking Medicare administrative, claims, and survey data, the MCBS collects comprehensive information on demographic and socioeconomic characteristics, health status, healthcare utilization, and medical costs from Medicare beneficiaries.

Study Population

This study included Medicare beneficiaries who were 65 years of age and over, lived in the community setting, had a diagnosis of dementia or had two or more dementia prescriptions with more than 60-days supply, and had continuous coverage of Medicare Part A, B, and D. Medicare beneficiaries who were enrolled in the

TABLE 1 | Characteristics of older adults with dementia and their use of antipsychotics (Weighted *n* = 4,953,945).

	Total	Antipsychotic use		
	***n* = 4,953,945**	**No**	**Yes**	***p***
		***n* = 4,301,145**	***n* = 652,799**	
—	%	%	%	
Age	—	—	—	0.7871
65–74	18.65	18.27	21.14	—
75–84	36.64	36.80	35.61	—
85+	44.71	44.93	43.25	—
Gender	—	—	—	0.9623
Female	66.74	66.78	66.50	—
Male	33.26	33.22	33.50	—
Race/ethnicity	—	—	—	0.0305
Non-Hispanic white	78.66	79.76	71.43	—
Non-Hispanic black	9.67	8.91	14.70	—
Hispanic	7.22	6.59	11.40	—
Other	4.45	4.75	2.47	—
Education	—	—	—	0.7191
Less than high school	25.72	25.92	24.28	—
High school graduate	32.93	32.93	32.96	—
Some college	19.14	19.66	15.49	—
College graduate	22.21	21.50	27.27	—
Marital status	—	—	—	0.0249
Married	37.78	39.62	25.60	—
Widowed	46.55	45.53	53.36	—
Single	15.67	14.86	21.04	—
Income	—	—	—	0.8951
<$10,000 per year	17.09	16.81	18.94	—
$10,000–19,999 per year	30.95	31.31	28.57	—
$20,000–39,999 per year	23.79	23.85	23.39	—
≥ $40,000 per year	28.17	28.03	29.11	—
Residence	—	—	—	0.1354
Metropolitan	77.59	76.81	82.74	—
Non-metropolitan	22.41	23.19	17.26	—
Census region	—	—	—	0.4381
Northeast	20.14	20.64	16.81	—
Midwest	24.05	24.61	20.34	—
South	41.76	40.76	48.40	—
West	14.05	13.99	14.45	—
CCI	—	—	—	0.4468
0	22.50	22.32	23.70	—
1	21.32	20.64	25.84	—
2	14.56	14.53	14.81	—
3+	41.61	42.52	35.65	—
—	Mean ± SD	Mean ± SD	Mean ± SD	*p*
Healthcare utilization				
Inpatient	0.58 ± 0.04	0.53 ± 0.04	0.91 ± 0.11	0.0011
Outpatient	6.72 ± 0.34	6.90 ± 0.36	5.55 ± 0.53	0.0189
ER admission	1.25 ± 0.07	1.17 ± 0.07	1.77 ± 0.19	0.0016
Medical costs ($)				
Total costs	53,336 ± 2,050	50,299 ± 2,172	73,345 ± 4,793	<0.0001
Medicare costs	23,053 ± 1,258	22,000 ± 1,378	29,990 ± 2,808	0.0100
OOP costs	14,942 ± 947	13,902 ± 966	21,792 ± 2,656	0.0057

CCI, charlson comorbidity index; ER, emergency room; OOP, out-of-pocket; SD, standard deviation.

health maintenance organization and had a diagnosis of schizophrenia, bipolar disorder, Huntingon's disease, or Tourette's syndrome were excluded.

Measurement

Antipsychotic use was measured based on Medicare Part D prescription events, as defined by the Pharmacy Quality Alliance (PQA). Antipsychotics measured in this study included aripiprazole, asenapine, brexpiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimavanserin, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and ziprasidone. Cumulative days of antipsychotic use were calculated as the total number of days of antipsychotic use in a measurement year. Dementia was

TABLE 2 | Factors associated with antipsychotic use in older adults with dementia.

	OR	95% CI
Age		
65–74	Ref	—
75–84	0.81	(0.37, 1.78)
85+	0.57	(0.26, 1.27)
Gender		
Female	Ref	—
Male	1.20	(0.65, 2.23)
Race/ethnicity		
Non-Hispanic white	Ref	—
Non-Hispanic black	1.87	(0.84, 4.20)
Hispanic	2.90	(1.45, 5.78)
Other	0.71	(0.24, 2.10)
Education		
Less than high school	Ref	—
High school graduate	1.42	(0.68, 2.99)
Some college	0.89	(0.40, 1.99)
College graduate	1.75	(0.70, 4.37)
Marital status		
Married	Ref	—
Widowed	3.52	(1.46, 8.48)
Single	3.25	(1.53, 6.87)
Income		
<$10,000 per year	Ref	—
$10,000–19,999 per year	1.12	(0.59, 2.12)
$20,000–39,999 per year	1.62	(0.84, 3.10)
≥ $40,000 per year	2.08	(0.98, 4.41)
Residence		
Metropolitan	Ref	—
Non-metropolitan	0.56	(0.30, 1.08)
Census region		
Northeast	Ref	—
Midwest	1.18	(0.48, 2.87)
South	1.91	(0.90, 4.03)
West	1.48	(0.67, 3.28)
CCI		
0	Ref	—
1	1.32	(0.65, 2.70)
2	0.78	(0.39, 1.58)
3+	0.77	(0.43, 1.38)

CCI, charlson comorbidity index; OR, odds ratio; CI, confidence interval.

measured using the relevant 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes from Medicare Part A and B claims. Healthcare utilization was measured as inpatient services, outpatient services, and emergency room (ER) visits and was collected from Medicare Part A and B claims. Total medical costs were collected from Medicare claims and self-reports. Total costs were further classified as Medicare and out-of-pocket (OOP) costs based on different payers. Medical costs in different years were adjusted to 2017 dollars using the consumer price index of medical care services. Covariates considered in this study included age, gender, race/ethnicity, education, marital status, income, residence, census region, and comorbidity.

Statistical Analyses

Characteristics of the study population were compared between users and non-users of antipsychotics by the Chi-square test. The t-test was used to compare healthcare utilization and medical costs between users and non-users of antipsychotics. The logistic regression model was used to identify factors associated with antipsychotic use. Healthcare utilization was analyzed using the negative binomial regression for count data. Medical costs were analyzed using the generalized linear model with a log link and gamma distribution. Survey sampling weights were applied to generate national estimates. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

After applying the inclusion and exclusion criteria, 4,953,945 (weighted number) older adults with dementia were included in this study. The majority of respondents were at least 85 years old (44.71%), female (66.74%), non-Hispanic whites (78.66%), high school graduate (32.93%), widowed (46.55%), had an annual household income between $10,000 and $19,999 (30.95%), lived in metropolitan areas (77.59%), lived in the South (41.76%), and had a Charlson comorbidity index (CCI) of three and higher (41.61%). (**Table 1**). Among older adults with dementia, 13.18% (weighted number = 652,799) used antipsychotics. Compared to those who did not use antipsychotics, antipsychotic users were more likely to be racial and ethnic minorities (p = 0.0305) and not married (p = 0.0249). (**Table 1**). Among users of antipsychotics, 16.51% used 1–30 days, 13.39% used 31–90 days, 19.04% used 91–180 days, 14.29% used 181–300 days, and 36.76% used more than 300 days.

Ethnicity and marital status were two characteristics associated with antipsychotic use in older adults with dementia identified in this study. Compared to non-Hispanic whites, Hispanics were significantly more likely to use antipsychotics [OR (odds ratio): 2.90; 95% CI (confidence interval): 1.45, 5.78] (**Table 2**). Widowed (OR: 3.52; 95% CI: 1.46, 8.48) and single older adults (OR: 3.25; 95% CI: 1.53, 6.87) were significantly more likely to use antipsychotics, compared to those who were married. (**Table 2**). Age, gender, education level, annual income, residence, census region, and comorbidity were not found to be associated with antipsychotic use.

The annual number of inpatient visits was 0.58 (SD = 0.04), outpatient visits were 6.72 (SD = 0.34), and ER visits were 1.25 (SD = 0.07) on average among older adults with dementia. (**Table 1**). After controlling for covariates, antipsychotic use was associated with significantly more inpatient visits (IRR [incidence rate ratio]: 2.11; 95% CI: 1.53, 2.90) and more ER visits (IRR: 1.61; 95% CI 1.21, 2.13). (**Figure 1**). The magnitude of the association between antipsychotic use and healthcare utilization was decreased with the increase in cumulative days of antipsychotic use (**Figure 1**).

The annual total costs were $53,336 (SD = $2,050), Medicare costs were $23,053 (SD = $1,258), and OOP cost were $14,942 (SD = $947) on average among older adults with dementia (**Table 1**). After controlling for covariates, antipsychotic use was associated with significantly higher total costs (β: 0.53; 95% CI: 0.36, 0.71), higher Medicare costs (β: 0.49; 95% CI

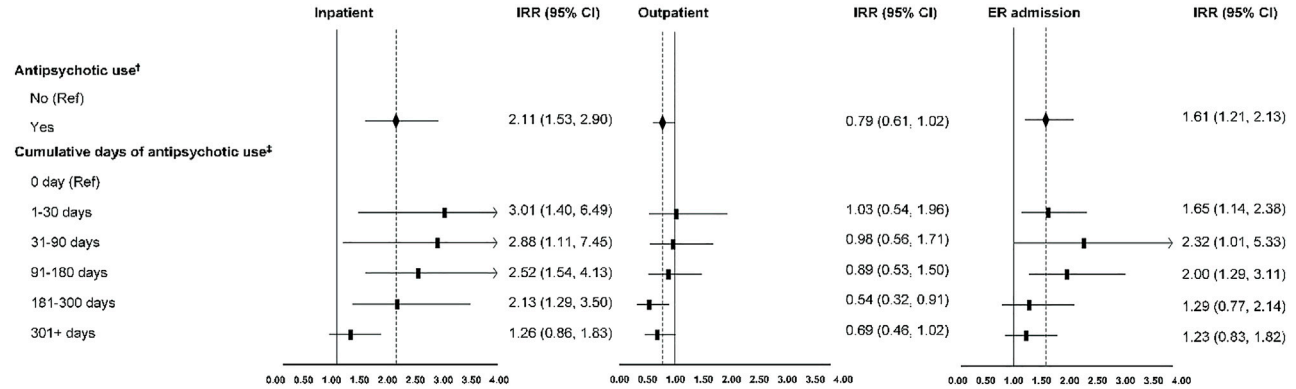

FIGURE 1 | Healthcare utilization associated with antipsychotic use in older adults with dementia. ER indicates emergency room; IRR, incidence rate ratio; CI, confidence interval. †, ‡: Covariates adjusted (age, gender, race/ethnicity, education, marital status, income, residence, census region, and comorbidity).

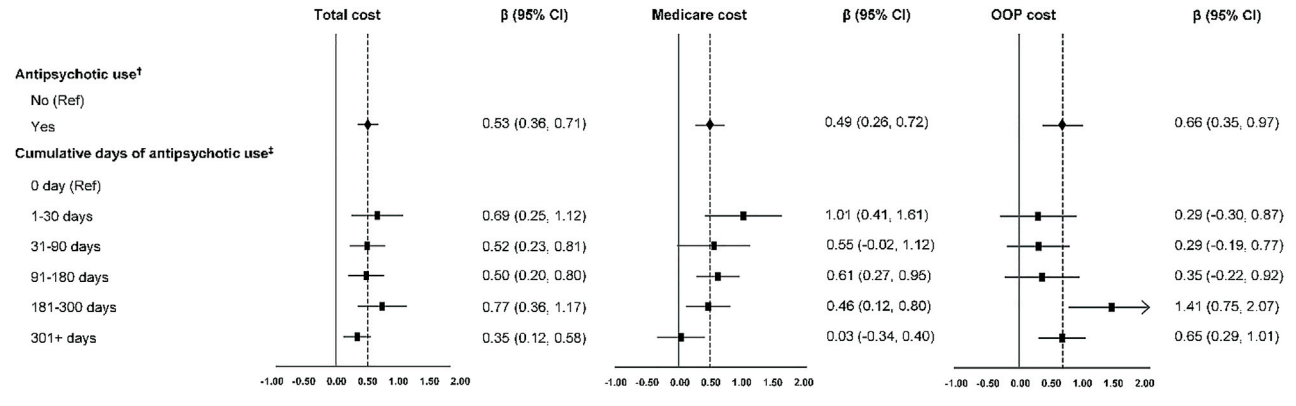

FIGURE 2 | Medical costs associated with antipsychotic use in older adults with dementia. OOP indicates out-of-pocket; CI, confidence interval. †, ‡: Covariates adjusted (age, gender, race/ethnicity, education, marital status, income, residence, census region, and comorbidity).

0.26, 0.72), and higher OOP costs (β: 0.66; 95% CI: 0.35, 0.97) (**Figure 2**). The magnitude of the association between antipsychotic use and total and Medicare costs was decreased with the increase in cumulative days of antipsychotic use. However, the magnitude of the association between antipsychotic use and OOP costs was increased with the increase in cumulative days of antipsychotic use (**Figure 2**).

DISCUSSION

This study identified ethnicity as a factor associated with antipsychotic use among older adults with dementia. Specifically, we found that Hispanics were three-fold more likely to use antipsychotic agents compared to non-Hispanic whites. This is consistent with Xiong et al.'s study which found that Hispanics were 1.4-times more likely to take antipsychotics compared to non-Hispanic whites (Xiong et al., 2015). This ethnic disparity could be explained by greater dementia severity, more prevalent BPSD symptoms, language barrier, and cultural norm (Ferguson and Candib, 2002; Xiong et al., 2015). Xiong et al. found that Hispanics were more likely to have a higher severity of dementia, as well as a higher prevalence of BPSD symptoms across all dementia severity (Xiong et al., 2015). Additionally, the language barrier might limit patient-provider communication among Hispanic patients. Ferguson and Candib found that minority patients not proficient in English were more likely to have the quality of patient-provider communication and relationship adversely affected as the language barrier might prevent the establishment of rapport, the receipt of sufficient information, and patient participation in medical decision-making (Ferguson and Candib, 2002). For example, clinicians might have difficulties when communicating with Spanish-speaking patients to identify potentially inappropriate use of antipsychotics and thus might be less likely to engage in deprescribing activities. Furthermore, Spanish-speaking patients and/or caregivers might not be able to understand the risk-benefit information communicated to them, with regards to the use of antipsychotics in BPSD. The cultural norm of self-prescription could explain the higher likelihood of antipsychotic use in Hispanics with dementia (Coffman et al., 2008). As Central and South America allow

the unrestricted sale of medications that would otherwise be strictly regulated in the U.S., self-prescribing and use of medications among resident Hispanics for self-care are highly prevalent (Coffman et al., 2008). Therefore, Hispanics with dementia might be less willing to try non-pharmacological therapies as they find more comfort in using antipsychotics or perceive antipsychotics as being more effective.

In addition to being of Hispanic ethnicity, this study found that being widowed and single were associated with a higher likelihood of using antipsychotics, compared to those who were married. Differences in marital status in antipsychotic use in older adults with dementia can be explained by the type of caregiver providing dementia care. The main caregiver of a married individual is usually the spouse. For a widowed or single individual, the main caregiver can be a child, a family member, a friend, or a nurse. Previous studies found differences in care provided by adult-child and spousal caregivers (Reed et al., 2014; Rigby et al., 2019). Reed et al. reported that adult-child caregivers providing care to patients with Alzheimer's disease, spent less overall caregiving time (e.g., assisting with basic activities of daily living and supervising patients) compared to spousal caregivers (Reed et al., 2014). Rigby et al. reported that adult-child caregivers who provided care to patients with Lewy body dementia saw them less often compared to spousal caregivers (Rigby et al., 2019). Due to the time and effort involved in non-pharmacological treatments, a caregiver other than the spouse might be more willing to consider pharmacological treatments on dementia patients with behavior issues.

The use of antipsychotics was found to be associated with more inpatient and ER visits. Adverse events, especially serious ones, associated with antipsychotic use in patients with dementia might contribute to the increased inpatients and ER visits identified in this study. Rochon *et al.* found that antipsychotic use was associated with a higher likelihood of developing serious adverse events (defined as hospitalization or death) within 30 days of use, among community-dwelling older adults with dementia (Rochon et al., 2008). Serious adverse events contributing to the acute care hospital admissions within 30 days of antipsychotic use included fall or hip fracture, cerebrovascular event, extrapyramidal symptoms, and other adverse events (Rochon et al., 2008). This study found a decreasing trend in healthcare utilization with the increase in cumulative days of antipsychotic use. Previous studies found that the risk of serious adverse events associated with antipsychotics was the highest within the first few weeks of use (Ballard et al., 2011; Kales et al., 2015). Kales et al. reported that the mortality risk was 1.5-fold higher within the first 120 days of antipsychotic use and decreased in the following 60 days among older adults with dementia (Kales et al., 2015). The increased cerebrovascular adverse events were only significant within the first week of antipsychotic use but not significant over a longer duration of use, among older antipsychotic users (Ballard et al., 2011). This association might explain the higher healthcare utilization within the first 30 days of antipsychotic use found in this study.

This study also found that the use of antipsychotics among older adults with dementia was associated with a higher economic burden. This is consistent with the cost-benefit analysis of a clinical trial evaluating the effectiveness of second-generation antipsychotics in treating BPSD symptoms among outpatients with Alzheimer's disease. (Rosenheck et al., 2007). Total healthcare costs were found to be significantly higher with the users of second-generation antipsychotics, compared to non-users. (Rosenheck et al., 2007). Our study further included older adults with other types of dementia and measured costs from different payers. With cumulative days of use, our study observed the highest total and Medicare costs within the first 30-days of use, which then decreased with continued use of antipsychotics. To our knowledge, this is a novel finding in the literature, since no existing studies have evaluated the effects of cumulative antipsychotic use on medical costs. The higher economic burden within the first 30 days could be related to the higher rates of mortality and cerebrovascular events in the short term and its associated healthcare utilization (Ballard et al., 2011).

The significant increase in clinical and economic burden associated with antipsychotic use observed in this study provides real-world evidence to support deprescribing these agents in older adults with dementia. Deprescribing refers to the planned discontinuation or dose reduction, under medical supervision, of a medication when the benefits of continued use or at the current dose no longer outweigh the risks (Bjerre et al., 2018). Based on our findings, deprescribing efforts might be most beneficial when performed with short-term use of antipsychotics. This is consistent with the recommendation from the 2016 American Psychiatric Association Practice Guideline on the use of antipsychotics to treat BPSD, which suggests that antipsychotics should be tapered and discontinued if patients have no clinically significant response after a four-week trial (Reus et al., 2016). Additionally, consideration of deprescribing is also recommended in patients who experience clinically significant adverse events any time after use and/or in those who have adequately responded to treatment after 4 months of use (Reus et al., 2016). The guidelines also highlight the importance of engaging patients and/or their caregivers when making clinical decisions regarding using and deprescribing antipsychotic agents (Reus et al., 2016). Based on the results of existing discontinuation studies, tapering and stopping antipsychotics can be done safely without symptom recurrence in many patients (Ballard et al., 2009; Reus et al., 2016). However, monthly or more frequent reassessment of patients undergoing tapering up to 4 months following successful discontinuation of these agents, is prudent to monitor for recurrence of BPSD symptoms (Reus et al., 2016).

As our study has highlighted that individuals of Hispanic ethnicity and those who are single or widowed are more likely to use antipsychotic agents, increased attention should be paid when prescribing antipsychotics to these patients. For example, healthcare providers should address language barriers by ensuring the availability of professional interpreters at medical visits for Hispanic patients who speak limited English and collaborate with caregivers to implement non-pharmacological interventions prior to initiating antipsychotic therapy when feasible. Furthermore, these individuals might be targets for

initial deprescribing efforts. As the finding from our study suggests that successful discontinuation of antipsychotics among older adults with dementia might not only reduce adverse events associated with antipsychotic use, but might also reduce clinical and economic burden.

This study has some strengths and limitations. To our knowledge, this is the first study conducted in the U.S. assessing the impact of antipsychotic use on healthcare utilization and costs among older adults with dementia. This study further examined cumulative days of antipsychotic use to support clinical practice in deprescribing efforts. Among the limitations, this study may not have identified all dementia patients since dementia can be under-diagnosed or undiagnosed. Therefore, those who have not seeked care would not be captured in Medicare claims. In addition, the stage and severity of dementia and BPSD cannot be measured based on ICD-10 codes. Second, different types of antipsychotics were not examined in this study, and the dispensed prescription was used as a proxy for medication use. Third, this study was conducted on residents in the community rather than facility settings. Finally, indirect costs of antipsychotic use (e.g., productivity loss of family members caring for patients) were not assessed.

CONCLUSION

Antipsychotic agents should be used judiciously in older adults with dementia due to the increased clinical and economic burden. Factors associated with antipsychotic use included being of Hispanic ethnicity and being of a widowed or single status. Healthcare utilization and medical costs were significantly increased with antipsychotic use. With the increase in cumulative days of antipsychotic use, the magnitude of clinical and economic burden was decreased. The significant clinical and economic burdens associated with users of antipsychotics, especially short-term users, provide real-world evidence to inform clinical practice on deprescribing antipsychotics among community-dwelling geriatric dementia patients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data will not be made readily available for the privacy of the participants. Requests to access these datasets should be directed to: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS; MCBS@cms.hhs.gov.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Tennessee Health Science Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SH and ML: concept and design. ML: acquisition, analysis, or interpretation of data. SH, JY, ZL, and ML: drafting of the manuscript and critical revision of the manuscript for important intellectual content. ML: statistical analysis. All authors contributed to the article and approved the submitted version.

REFERENCES

Alzheimer's Association (2020). Alzheimer's Disease Facts and Figures. *Alzheimers Dement J. Alzheimers Assoc.* 16 (3), 391–460. doi:10.1002/alz.12068

American Geriatrics Society Beers Criteria® Update Expert Panel (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J. Am. Geriatr. Soc.* 67 (4), 674–694. doi:10.1111/jgs.15767

Ballard, C., Creese, B., Corbett, A., and Aarsland, D. (2011). Atypical Antipsychotics for the Treatment of Behavioral and Psychological Symptoms in Dementia, with a Particular Focus on Longer Term Outcomes and Mortality. *Expert Opin. Drug Saf.* 10 (1), 35–43. doi:10.1517/14740338.2010.506711

Ballard, C., Hanney, M. L., Theodoulou, M., Douglas, S., McShane, R., Kossakowski, K., et al. (2009). The Dementia Antipsychotic Withdrawal Trial (DART-AD): Long-Term Follow-Up of a Randomised Placebo-Controlled Trial. *Lancet Neurol.* 8 (2), 151–157. doi:10.1016/S1474-4422(08)70295-3

Bjerre, L. M., Farrell, B., Hogel, M., Graham, L., Lemay, G., McCarthy, L., et al. (2018). Deprescribing Antipsychotics for Behavioural and Psychological Symptoms of Dementia and Insomnia: Evidence-Based Clinical Practice Guideline. *Can. Fam. Physician* 64 (1), 17–27.

Coffman, M. J., Shobe, M. A., and O'Connell, B. (2008). Self-Prescription Practices in Recent Latino Immigrants. *Public Health Nurs.* 25 (3), 203–211. doi:10.1111/j.1525-1446.2008.00697.x

Ferguson, W. J., and Candib, L. M. (2002). Culture, Language, and the Doctor-Patient Relationship. *Fam. Med.* 34 (5), 353–361.

Kales, H. C., Gitlin, L. N., and Lyketsos, C. G. (2015). Assessment and Management of Behavioral and Psychological Symptoms of Dementia. *BMJ* 350, h369. doi:10.1136/bmj.h369

Kim, H. M., Chiang, C., and Kales, H. C. (2011). After the Black Box Warning: Predictors of Psychotropic Treatment Choices for Older Patients with Dementia. *Psychiatr. Serv.* 62 (10), 1207–1214. doi:10.1176/ps.62.10.pss6210_1207

Kirkham, J., Sherman, C., Velkers, C., Maxwell, C., Gill, S., Rochon, P., et al. (2017). Antipsychotic Use in Dementia. *Can. J. Psychiatry* 62 (3), 170–181. doi:10.1177/0706743716673321

Liperoti, R., Pedone, C., and Corsonello, A. (2008). Antipsychotics for the Treatment of Behavioral and Psychological Symptoms of Dementia (BPSD). *Curr. Neuropharmacol* 6 (2), 117–124. doi:10.2174/157015908784533860

Maust, D. T., Kim, H. M., Seyfried, L. S., Chiang, C., Kavanagh, J., Schneider, L. S., et al. (2015). Antipsychotics, Other Psychotropics, and the Risk of Death in Patients with Dementia: Number Needed to Harm. *JAMA Psychiatry* 72 (5), 438–445. doi:10.1001/jamapsychiatry.2014.3018

Medicare Current Beneficiary Survey (MCBS) (2019). Medicare Current Beneficiary Survey (MCBS) | CMS Published December 6, 2019. Centers for Medicare & Medicaid Services (online). Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS (Accessed April 24, 2020).

Raivio, M. M., Laurila, J. V., Strandberg, T. E., Tilvis, R. S., and Pitkälä, K. H. (2007). Neither atypical Nor Conventional Antipsychotics Increase Mortality or Hospital Admissions Among Elderly Patients with Dementia: a Two-Year Prospective Study. *Am. J. Geriatr. Psychiatry* 15 (5), 416–424. doi:10.1097/JGP.0b013e31802d0b00

Reed, C., Belger, M., Dell'agnello, G., Wimo, A., Argimon, J. M., Bruno, G., et al. (2014). Caregiver Burden in Alzheimer's Disease: Differential Associations in Adult-Child and Spousal Caregivers in the GERAS Observational Study. *Dement Geriatr. Cogn. Dis. Extra* 4 (1), 51–64. doi:10.1159/000358234

Reus, V. I., Fochtmann, L. J., Eyler, A. E., Hilty, D. M., Horvitz-Lennon, M., Jibson, M. D., et al. (2016). The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia. *Am. J. Psychiatry* 173 (5), 543–546. doi:10.1176/appi.ajp.2015.173501

Rigby, T., Ashwill, R. T., Johnson, D. K., and Galvin, J. E. (2019). Differences in the Experience of Caregiving between Spouse and Adult Child Caregivers in Dementia with Lewy Bodies. *Innov. Aging* 3 (3), igz027. doi:10.1093/geroni/igz027

Rochon, P. A., Normand, S. L., Gomes, T., Gill, S. S., Anderson, G. M., Melo, M., et al. (2008). Antipsychotic Therapy and Short-Term Serious Events in Older Adults with Dementia. *Arch. Intern. Med.* 168 (10), 1090–1096. doi:10.1001/archinte.168.10.1090

Rosenheck, R. A., Leslie, D. L., Sindelar, J. L., Miller, E. A., Tariot, P. N., Dagerman, K. S., et al. (2007). Cost-benefit Analysis of Second-Generation Antipsychotics and Placebo in a Randomized Trial of the Treatment of Psychosis and Aggression in Alzheimer Disease. *Arch. Gen. Psychiatry* 64 (11), 1259–1268. doi:10.1001/archpsyc.64.11.1259

Sepassi, A., and Watanabe, J. H. (2019). Emergency Department Visits for Psychotropic-Related Adverse Drug Events in Older Adults with Alzheimer Disease, 2013-2014. *Ann. Pharmacother.* 53 (12), 1173–1183. doi:10.1177/1060028019866927

Tampi, R. R., Tampi, D. J., Balachandran, S., and Srinivasan, S. (2016). Antipsychotic Use in Dementia: A Systematic Review of Benefits and Risks from Meta-Analyses. *Ther. Adv. Chronic Dis.* 7 (5), 229–245. doi:10.1177/2040622316658463

van der Flier, W. M., and Scheltens, P. (2005). Epidemiology and Risk Factors of Dementia. *J. Neurol. Neurosurg. Psychiatry* 76 (Suppl. 5), v2–7. doi:10.1136/jnnp.2005.082867

Xiong, G. L., Filshtein, T., Beckett, L. A., and Hinton, L. (2015). Antipsychotic Use in a Diverse Population with Dementia: A Retrospective Review of the National Alzheimer's Coordinating Center Database. *J. Neuropsychiatry Clin. Neurosci.* 27 (4), 326–332. doi:10.1176/appi.neuropsych.15010020

Zhai, Y., Yin, S., and Zhang, D. (2016). Association between Antipsychotic Drugs and Mortality in Older Persons with Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J. Alzheimers Dis.* 52 (2), 631–639. doi:10.3233/JAD-151207

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Cost-Effectiveness Analysis of PEG-rhG-CSF as Primary Prophylaxis to Chemotherapy-Induced Neutropenia in Women With Breast Cancer in China: Results Based on Real-World Data

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Background: Pegylated recombinant human granulocyte colony-stimulating factors (PEG-rhG-CSFs) are more commonly and widely used than recombinant human granulocyte colony-stimulating factors (rhG-CSFs) in preventing chemotherapy-induced neutropenia in patients with stage II-IV breast cancer. To reduce the financial burden on these patients, the corresponding medical insurance directory needs to be revised.

Objectives: To evaluate the cost-effectiveness of PEG-rhG-CSF versus rhG-CSF in patients with stage II-IV breast cancer in central China.

Methods: Two Markov models, a chemotherapy model and a post-chemotherapy model, were developed to study the effects and costs, with a time horizon of 12 weeks and 35 years, respectively. Cost and probability input data were primarily obtained from a retrospective real-world study conducted in five tertiary hospitals. Propensity score matching was adopted to overcome retrospective bias. Other parameters were extracted from literature as well as advice from clinical experts. Univariate and probabilistic sensitivity analyses were conducted.

Results: In the first chemotherapy model, PEG-rhG-CSF was associated with fewer episodes of febrile neutropenia (FN) (N = 19 per 1000 patients treated), infections (N = 24 per 1000 patients treated) and deaths (N = 2 per 1000 patients treated), but higher costs (¥36 more per patient treated). The post-chemotherapy model indicated that PEG-rhG-CSF led to higher gains in quality-adjusted life years (QALYs) (11.695 versus 11.516) in comparison to rhG-CSF. Sensitivity analysis showed that the cost of PEG-rhG-CSF had the greatest impact on the incremental costs, and incremental QALYs were very sensitive to the risk of RDI <85%. The probability of PEG-rhG-CSF being cost-effective compared to

rhG-CSF was 66% at the willingness to pay (WTP) thresholds of ¥72,371 per QALY gained.

Conclusion: According to this economic evaluation based on real-world data, PEG-rhG-CSF may be considered as a more cost-effective strategy relative to rhG-CSF for stage II-IV breast cancer patients in central China. However, to reflect a national perspective, further evidence is needed using data from larger-scale studies.

Keywords: cost-effectiveness, PEG-rhG-CSF, chemotherapy-induced neutropenia, breast cancer, real-world

1 INTRODUCTION

The incidence of breast cancer tops the female cancers in China, and the age standardization incidence rate (ASIR) is increasing every year (World Health Organization, 2020). In 2018, 98000 women died of breast cancer in China, accounting for 15% of all cancer-related deaths in women (Bray et al., 2018). In the era of precision medicine, chemotherapy remains the cornerstone of treatment for patients with breast cancer (Chinese Society of Clinical Oncology Guidance Working Committee, 2017), not only because adjuvant chemotherapy significantly improves disease-free and overall survival, but also due to the chemotherapy directly leads to improved patient survival (Esteva et al., 2001; Peto et al., 2012). Accompanying the chemotherapy, however, neutropenia is a common and frequent side effect, as well as a major risk factor for infection-related morbidity and mortality (Donadieu et al., 2011). Prolonged and severe neutropenia may lead to serious toxicity such as febrile neutropenia (FN). The presence of FN in cancer patients may lead to reduced dose intensity (RDI), worsening clinical efficacy, as well as severe infection complications, even death (Chinese Society of Clinical Oncology Guidance Working Committee, 2017). Under the current medical conditions, when the patient's neutropenia lasts for >21 days, the incidence of infection is significantly increased (Chinese Society of Hematology, 2020). Consequently, the patient's quality of life is affected, and the clinical efficacy and cost-effectiveness of chemotherapy may be compromised (Lathia et al., 2013).

To counteract the negative impact of neutropenia, short and long acting granulocyte-colony stimulating factors (G-CSFs) are used to enhance the proliferation, differentiation, and maturation of neutrophils (Knudsen et al., 2011), thereby reducing the duration and severity of neutropenia, as well as the incidence of FN and infection-related mortality (Kuderer et al., 2007; Wang et al., 2015). The Chinese Society of Clinical Oncology recommends using G-CSFs as primary prophylaxis with chemotherapy regimens associated with a ≥20% incidence of FN (Chinese Society of Clinical Oncology Guidance Working Committee, 2017). Some randomized controlled trials (RCTs) in China also demonstrated that both short and long acting G-CSFs showed equal reduction in the incidence of FN (Sheng et al., 2015; Jiang et al., 2018; Xie et al., 2018; Liu et al., 2019), although there is no economic evidence. Currently, long-acting G-CSFs (PEG-rhG-CSFs) are more often used than short-acting G-CSFs (rhG-CSFs).

Although several cost-effectiveness analyses evaluating G-CSFs have been published (Akpo et al., 2017; Gao and Li, 2018; Li-Tian et al., 2019; Xia et al., 2020), all of them assumed a cost-effective benefit associated with PEG-rhG-CSFs based on RCTs.

The objective of this study was to determine whether primary prophylaxis against FN and related infections using either PEG-rhG-CSFs or rhG-CSFs in female breast cancer patients undergoing a four-cycle TC (docetaxel and cyclophosphamide) chemotherapy is cost-effective from a real-world setting.

2 MATERIALS AND METHODS

Model Design

A mathematical model was developed in Excel (Microsoft 2016) to estimate the health benefits and costs of using PEG-rhG-CSF compared with rhG-CSF as the primary prophylaxis in two hypothetical cohorts of women with stage II, III, IV breast cancer undergoing chemotherapy. Two Markov models were generated, one tracked on-chemotherapy cycles and neutropenia-related complications (FN and infection) (model 1) and another captured the impact of RDI on long-term survival (model 2). All patients entered the model at the average age of 45 years, and in the state labeled "chemotherapy" upon administration of chemotherapy agents, and G-CSFs (PEG-rhG-CSF or rhG-CSF) on day 2 of each chemotherapy cycle. The costs of treatment were the actual charges of medical services, and were estimated from the Chinese healthcare system perspective, reported in 2019 in Chinese yuan. Based on transition probabilities, the patients either moved to chemotherapy-related complication health states or remained in their current health state.

For the first model, a 3-week cycle length was defined for each of the four chemotherapy cycles, the time horizon in the chemotherapy model was 12 weeks accordingly, deaths associated with FN and infections were considered. No discounting was applied in this model. For the long-term survival model, the annual cycle was taken with a time horizon of 35 years, as the average life expectancy among the Chinese (including the breast cancer patients) is nearly 80 years, and the average age of the patients in our study was 45 years. In accordance with pharmacoeconomic evaluation guidelines (Liu, 2020), both costs and utilities were discounted at 5% each year.

Costs and clinical data were obtained through real-world, expert consultation and literature review. The two model structures are shown in **Figure 1**.

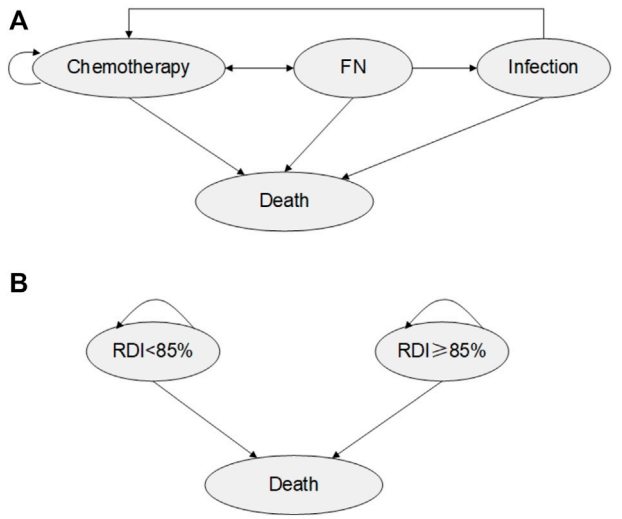

FIGURE 1 | Model Structure **(A)** Model 1: Chemotherapy Markov Model. **(B)** Model 2: Post-chemotherapy Markov model.

Real-World Data Collection

Clinical and cost data were obtained through a non-interventional, retrospective observational study of female breast cancer patients from five sites in Henan province, which have the largest population of breast cancer patients in China, and represent the characteristics of the target population of this study. As per the objective of the study, patients below 18 years of age and those with other cancers or underwent both G-CSFs were excluded.

Clinical data were collected from hospital administrative records, by retrospectively including all cases receiving rhG-CSF and a larger sample of patients receiving PEG-rhG-CSF, between January 2019 and December 2020. Patient-level data were de-identified to protect the privacy and sensitive information. Cost data included the total direct medical costs during the hospitalization for chemotherapy, including fees for drugs, examinations, tests, hospitalization, nursing, etc.

Propensity score matching (PSM) was conducted to overcome retrospective bias, by considering age, gender, type of health insurance, and the number of concomitant diseases. In this study, a 1:1 ratio between matched subjects was used. The means of propensity scores after matching were 0.52 for the PEG-rhG-CSF group and 0.49 for the rhG-CSF group. Meanwhile, the results of the data analysis such as mean age and mean costs after PSM adjustment were used as key inputs in the Markov model.

Model Inputs

2.1.1 Clinical Data

In the chemotherapy model, the main clinical input data was the incidence of FN from the collected real-world patient-level data. The risk of infection in the case of FN was estimated based on the Chinese guidelines for the clinical application of antibacterial drugs for agranulocytosis with fever (2020) (Chinese Society of Hematology, 2020). Some other inputs, utility data, and death rate were obtained through literature review. Additionally, because only limited data were obtainable from real-world data and local literature, eight expert oncologists were consulted to close the data gaps, especially for the cost of infection treatment. These experts were selected based on the hospital category (including general, oncology, and women's hospitals) and their experience with breast cancer. **Table 1** summarizes the parameter values and their sources.

The post-chemotherapy model mainly considered the impact of decreases in RDI on survival. As mentioned above, age and FN event as predictors of receiving RDI <85%. The risk of RDI <85% for the history of FN was calculated from the real-world data, and other model inputs were extracted from literatures. Breast cancer-specific mortality data by stage and age were accessed from the Chinese Cancer Registry Annual Report and all-cause mortality data from the National Bureau of Statistics of China. **Table 2** presents the list of parameters used in the post-chemotherapy model.

2.1.2 Costs

The unit cost for resource use related to G-CSFs, chemotherapy regimen, antibiotics/anti-fungals, and average hospitalization cost (including nursing, oncology ward, laboratory tests, examinations, etc.) were considered. Drug cost data (in 2019 CNY-¥) were derived from the local medical procurement platform, considering the average of the list price. Chemotherapy [docetaxel, 75 mg/m2 of body surface area (BSA), plus cyclophosphamide, 600 mg/m2] was administered every 21 days for four cycles. The expert consultation yielded data about the use of antimicrobials for the infections following FN, mainly bacteremia, gastrointestinal, urinary, cellulitis, and fungal infections (Dan-Li et al., 2015), which were estimated as a weighted average of the cost per treatment course, considering relative market share. Only inpatient costs were considered for FN. Simultaneously, it was assumed that the cost of FN and infection hospitalization did not differ between the two G-CSFs. The per cycle cost of hospitalization was obtained from the China Health Statistics Yearbook (2020), considering the mean of all listed medication costs. There were no costs imputed for the post-chemotherapy model. **Table 1** summarizes the unit cost populated in the first model.

2.1.3 Utilities

Utility levels for each health state in the chemotherapy and post-chemotherapy models were taken from the published literature (**Tables 1**, **2**). The estimated utility for the state of chemotherapy, FN/infection, breast cancer survivor during years one to five and after year five was 0.7, 0.33, 0.86, and 0.96 (Akpo et al., 2017). As a result of the lack of data on utility values for infection, these data were assumed to be equal to that of FN, according to Gao and Li (2018).

Sensitivity Analysis

Sensitivity analyses comprised univariate and probabilistic sensitivity analyses. One-way sensitivity analysis was adopted to test the variance of underlying parameter values and assumptions within the models. The variance of each parameter was set to either 95% confidence intervals (CI),

TABLE 1 | Summary of input parameters for the chemotherapy model.

Parameter	Base case value		Distribution for PSA	Source[a]
	PEG-rhG-CSF	rhG-CSF		
Transition probabilities				
Baseline of FN event across all chemotherapy cycles	0.0116	0.0404	Beta	A
Risk of infection in patients with FN	0.0547	0.547	Beta	B
Risk of death in patients with FN	0.034	0.034	Beta	Xia et al.
Risk of death if infection	0.034	0.034	Beta	C
Cost inputs (¥)				
G-CSF, per cycle	3315.74	734.34 (6d)	Gamma	A
Chemotherapy, per cycle				
Docetaxel	1792.74 (20mg/0.5 ml)		Gamma	A
Cyclophosphamide	120.75 (0.2g)		Gamma	A
FN inpatient, per patient	25000		Gamma	C
Infection if FN, per patient	50000		Gamma	C
Hospitalization(mean)	14811.10		Gamma	D
Utility inputs				
Chemotherapy	0.70		Beta	Akpo et al.
FN inpatient	0.33		Beta	Akpo et al.
Infection	0.33		Beta	Akpo et al.

G-CSF, granulocyte colony-stimulating factor; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis.

[a]A, real-world data; B, Chinese guidelines for the clinical application of antibacterial drugs for agranulocytosis with fever (2020); C, expert opinion; D, national data of health care from NBS (National Bureau of Statistics of China).

TABLE 2 | Summary of input parameters for the post-chemotherapy model.

Parameter	Base case value	Distribution for PSA	Source[a]
Risk of RDI<85% if FN	0.500	Beta (α,β = 191)	A
Risk of RDI<85%, age<65 years old, no FN	0.247	Beta (α = 289, β = 881)	Akpo et al.
RR of RDI<85% for age≥65 vs. <65 years old	1.380		Akpo et al.
OR of RDI<85%, FN vs. no FN	1.580		Akpo et al.
HR of survival associated with an RDI<85% vs. RDI≥85%	1.730		Gao et al.
Utility of breast cancer in years 1–5	0.860	Beta (α = 40, β = 6)	Akpo et al.
Utility of breast cancer in years >5	0.960	Beta (α = 367, β = 15)	Akpo et al.

[a]A, real-world data.

where data were available or varied by 15% (according to literature) except for the discount rate, which was set as 3 and 7% (Liu, 2020).

Probabilistic sensitivity analysis (PSA) was conducted with a Monte-Carlo simulation, and all the input parameters on cost-effectiveness outcomes were incorporated into the analysis. Beta and gamma distributions were assigned to each relevant parameter, respectively. One thousand Monte-Carlo simulations were conducted with the value of model inputs randomly drawn from parameter distributions. A cost-effectiveness acceptability curve (CEAC) was presented to show the cost-effectiveness probability of PEG-rhG-CSF for different levels of WTP per QALY gained.

3 RESULTS

Real-World Data

Patient-level real-world data were retrospectively collected from a sample of 926 patients receiving PEG-rhG-CSF and 898 patients receiving rhG-CSF in the selected hospitals. In this primary cohort, the average length of hospital stay in the long-acting (PEG-rhG-CSF) group was 2 days more than in the short-acting (rhG-CSF) group (mean 10.47 ± 7.47 days in the long-acting group and 8.95 ± 7.88 days in the short-acting group; $p < 0.01$), and was associated with more total costs per hospitalization (mean ¥17,079 ± ¥3,084 in the long-acting group and ¥14,086 ± ¥335 in the short-acting group; $p < 0.01$). Meanwhile, surgical rates were also slightly higher in the long-acting group (52.9% in the long-acting group and 40% in the short-acting group). No significant difference was observed in age (mean 48.80 ± 9.56 years in the long-acting group and 48.75 ± 9.96 years in the short-acting group), occupation (most were retirees) and health insurance type (most were urban and rural residents).

PSM resulted in the inclusion of 852 patients each in the intervention and comparator groups. The baseline characteristics were balanced after PSM adjustment, with no significant differences in age, marriage, occupation, insurance type, and the surgery rate between the two groups. The average length of hospital stay in the long-acting group was also 2 days more than in the short-acting

TABLE 3 | Cost-effectiveness analysis results.

Strategy	Costs, CNY¥	QALYs	Incremental cost, CNY¥	Incremental QALYs	ICER, CNY¥/QALY
Chemotherapy model					
PEG-rhG-CSF	146091	3.456	36	0.104	347
rhG-CSF	146055	3.352	—	—	—
Post-chemotherapy model					
PEG-rhG-CSF		11.695		0.179	
rhG-CSF		11.516		—	

ICER, Incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

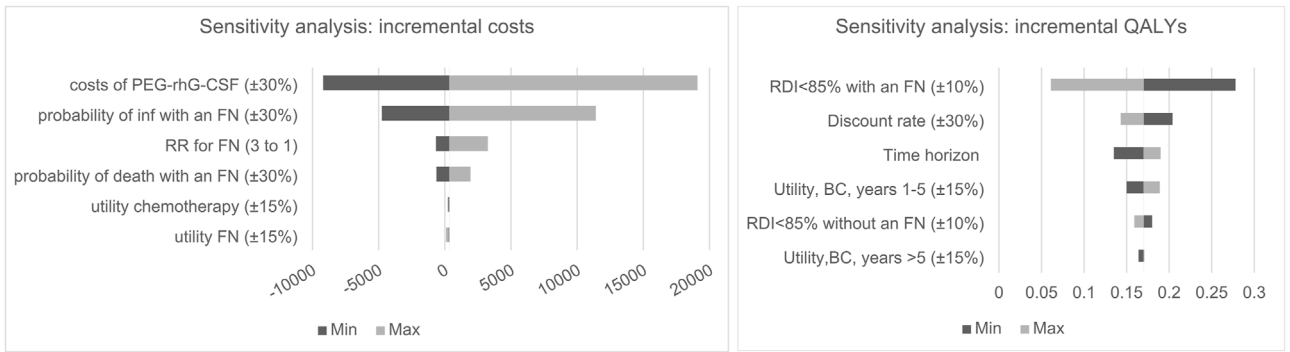

FIGURE 2 | One-way sensitivity analysis tornado diagram for incremental cost and QALY, BC, Breast cancer, inf, infection; FN, ferbrile eutropenia.

group. The total cost for single hospitalization was lower (mean ¥15,909 ± ¥4,960 in the long-acting group and ¥13,097 ± ¥2,968 in the short-acting group).

Base-Case Results

The cost-effectiveness results of primary prophylaxis with PEG-rhG-CSF compared to rhG-CSF for patients with stage II-IV breast cancer are presented in **Table 3**. Compared to rhG-CSF, treatment with PEG-rhG-CSF was associated with higher costs (¥36) and higher benefits, that included increased QALYs gained (0.104), and fewer cases of FN (19 vs. 61 per 1000 patients treated), infections (24 vs. 83 per 1000 patients treated) and deaths (2 vs. 8 per 1000 patients treated) in the chemotherapy model. **Table 3** also summarizes the effectiveness results from the post-chemotherapy model, which were estimated by a Monte Carlo simulation with 1000 iterations. Over the 35-year time horizon, administration of PEG-rhG-CSF was correlated with slightly higher gains in QALYs (11.695 vs 11.516) than rhG-CSF.

Sensitivity Analysis Results

3.1.1 Deterministic Sensitivity Analysis

One-way sensitivity analysis showed the impact of each model parameter on incremental costs and QALYs, as two tornado diagrams in **Figure 2**. For the scenarios within the possible ranges of model inputs, increasing FN and infection transition probabilities (30%) made PEG-rhG-CSF less costly compared to rhG-CSF. The cost of PEG-rhG-CSF had the greatest impact on the incremental costs, followed by the risk of infection in patients with FN and the risk of FN following chemotherapy. Incremental QALYs were most sensitive to variance in risk of RDI <85% with an FN. Additionally, QALYs gained decreased as the discount rate increased; and increased as the time horizon extended. Furthermore, QALYs gained increased as the utility for cancer survivors between one to 5 years increased.

3.1.2 Probabilistic Sensitivity Analysis

The PSA results are summarized as a scatterplot in **Figure 3**, which demonstrated a consistent finding of slightly better QALYs and higher costs for PEG-rhG-CSF in the majority of scenarios. The cost-effectiveness acceptability curve showed that at WTP of ¥72,371 per QALY (2020 GDP per capita to China), the probability that PEG-rhG-CSF would be considered a cost-effective alternative to rhG-CSF was 66% (**Supplementary Figure S1**).

In addition, the PSA for the post-chemotherapy model showed that administration of PEG-rhG-CSF led to greater gains in QALYs compared to rhG-CSF (PSA results of both models are listed in **Supplementary Table S1**).

4 DISCUSSION

The two G-CSFs compared in the present analysis were manufactured by Chinese pharmaceutical companies, and some clinical evidence demonstrated differences in effectiveness and safety (Liverani et al., 2014; Zhang et al.,

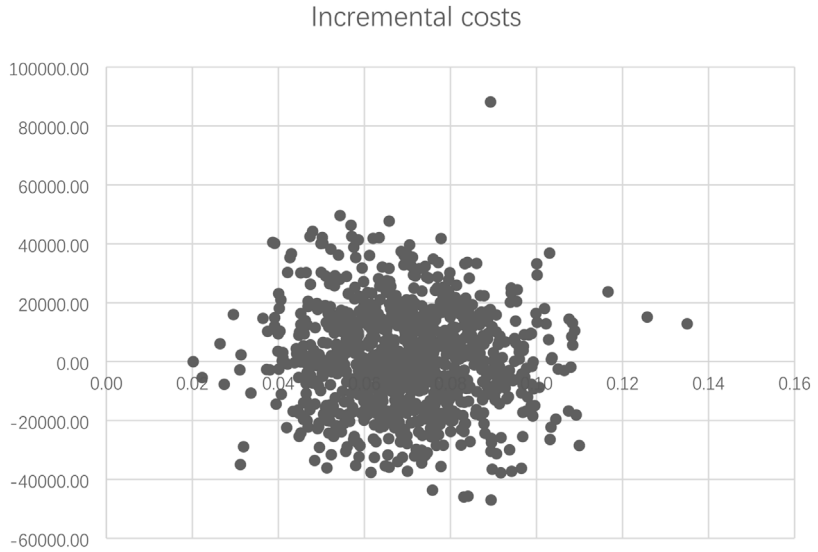

FIGURE 3 | Cost effectiveness plane for PEG-rhg-CSF compared to rhG-CSF.

2018a; Huang et al., 2018; Bongiovanni et al., 2019; Zhu et al., 2019; Ma et al., 2020; Huang et al., 2021). The PEG-rhG-CSF is recommended as a higher compliance treatment by current guidelines (Chinese Society of Clinical Oncology Guidance Working Committee, 2017). Nonetheless, real-world evidence and economic analysis results are increasingly recognized as an important and reasonable guide for reimbursement decision making in China since the 2017 national pricing negotiation on innovative medicines (Ming et al., 2019). Hence, this study evaluated the cost-effectiveness of PEG-rhG-CSF compared to rhG-CSF based on real-world data in China, with a particular focus on the incidence of FN, infections and RDI <85%. Additionally, QALYs gained were captured as standard measures of effect.

In our simulation modeling study, which applied PSM to real-world data, PEG-rhG-CSF was slightly inferior to rhG-CSF in terms of decreasing the risk of FN. This finding was consistent with published clinical studies (Garcia-Carbonero et al., 2001; Kuderer et al., 2007; Mhaskar et al., 2014). Moreover, the baseline characteristics of the cohort were similar to a previous multi-center randomized controlled phase Ⅳ clinical study in terms of age and chemotherapy regimens, and the conclusion was in line with the risk of FN (Jiang et al., 2018). There were four other health economic analyses in China based on clinical observations or randomized trials (Zhang et al., 2018b; Li-Tian et al., 2019; Xia et al., 2020; Zhang et al., 2020), and the findings were associated with a similar incidence of FN in the PEG-rhG-CSF group, while two of them showed different conclusions. One was using imported medicine (the price was much higher than the domestic drug) as the control group and the other came from a single center with small sample size (Li-Tian et al., 2019; Zhang et al., 2020).

Our analysis demonstrated that PEG-rhG-CSF was more cost-effective compared to rhG-CSF as primary prophylaxis under the WTP threshold of one-time GDP per capita. The result was similar to Xia et al. (2020), but different from Akpo et al. (2017), Gao and Li (2018), and Li-Tian et al. (2019), whose results showed that PEG-rhG-CSF strategy was cost-saving than rhG-CSF. Compared to randomized trials, our study showed that the incidence of FN for the short-acting group was higher than these studies, and the cost of the long-acting group was in excess of approximately ¥2,500, but the price gap in Akpo et al. (2017) and Gao and Li (2018) was zero. This may be one of the reasons why their results differed from ours.

Detailed sensitivity analyses of the key related parameters were performed to test the robustness of the cost-effectiveness conclusion. The base case analysis revealed that cost-savings were maximally influenced by the variation in the cost of PEG-rhG-CSF. As the average unit price of PEG-rhG-CSF is almost 15 times that of rhG-CSF in the current market, the analysis indicated that reducing the unit price of PEG-rhG-CSF by 30% would be cost-saving and dominant on ICER compared to the current price. Effectiveness results were mainly influenced by risk of RDI <85% with an FN, which was in line with Li-Tian et al. (2019) and Xia et al. (2020) who reported the parameter as a key driver of the cost-effectiveness for preventing FN after chemotherapy.

Furthermore, over a 35-year time horizon, PEG-rhG-CSF was likely (66%) to be associated with greater QALYs gained compared to rhG-CSF. Currently, oncology providers and pharmacists have more confidence in improving the usage of CSFs (Wong et al., 2020; Lapidari et al., 2021), and the short-acting agent is often used in patients with acute illness (Zhang et al., 2018b; Ma et al., 2020). Meanwhile, the experts we consulted indicated that the rhG-CSF is currently mainly used for emergency relief and short-term inpatients, and the probability of adoption is decreasing. Since both G-CSFs are covered by Chinese medical insurance, the rhG-CSF could be withdrawn from the health insurance directory to benefit a wider population of patients.

The strengths of this study include the use of data from real-world settings. The real-world data-based cost-effectiveness analysis clarified the impact of FN and related risk factors on its severity, as well as treatment effectiveness and economic impact of the management of neutropenia. These findings will be helpful in policymaking and health resource-planning.

This study had several limitations. First, the real-world data collected was from retrospective sources, due to reliance upon electronic health records, which could be less reliable than a prospective study (Ming et al., 2019), even though the PSM was adopted to surmount the potential bias. Second, the transition probabilities populated in each model were derived from limited empirical data source, some critical parameters and utility values were obtained from recommendations of the advisory group and international studies. Although we performed sensitivity analysis for the related parameters, the bias borne by this uncertainty might be minimized. Third, the post-chemotherapy costs were assumed to be zero according to the cost of G-CSFs, and associated costs were captured in the chemotherapy model. In addition, there is limited data from electronic records on the impact of RDI on resource utilization and related costs, as long-term costs cannot be accurately estimated. As the heterogeneous array of population were only Chinese, different geographic variations and ethnic groups can be included in further analysis.

In summary, this real-world data-based health economic evaluation showed that, comparing with rhG-CSF, PEG-rhG-CSF may be more cost-effective for the management of patients with stage II-IV breast cancer in the central region of China. Further data from national wide may be needed for a more comprehensive analysis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2020-KY-543).

AUTHOR CONTRIBUTIONS

All authors were involved with the conception and design of the evaluation, and JZ, GQ, YL, and SD mainly contributed in analyzing and interpreting the data, and drafting and critically revising the paper, others are mainly responsible for data collection and cleaning. All authors provided final approval and agreed to be accountable for the work reported herein.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Akpo, E. I. H., Jansen, I. R., Maes, E., and Simoens, S. (2017). Cost-Utility Analysis of Lipegfilgrastim Compared to Pegfilgrastim for the Prophylaxis of Chemotherapy-Induced Neutropenia in Patients with Stage II-IV Breast Cancer. *Front. Pharmacol.* 8, 614. doi:10.3389/fphar.2017.00614

Bongiovanni, A., Recine, F., Fausti, V., Rossi, B., Mercatali, L., Liverani, C., et al. (2019). Clinical Role of Filgrastim in the Management of Patients at Risk of Prolonged Severe Neutropenia: An Evidence-Based Review. *Int. J. Clin. Pract.* 73, e13404. doi:10.1111/ijcp.13404

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., and Jemal, A. (2018). Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* 68, 394–424. doi:10.3322/caac.21492

China Health Statistics Yearbook (2020). Data Stats. Available at: https://data.stats.gov.cn/easyquery.htm?cn=C01 (Accessed January1, , 2021).

Chinese Society of Clinical Oncology Guidance Working Committee (2017). Guidelines for Standardizedmanagement of Neutropenia Induced by Chemotherapy and Radiotherapy. *Zhonghua Zhong Liu Za Zhi* 39, 868–878. doi:10.3760/cma.j.issn.0253-3766.2017.11.011

Chinese Society of Hematology (2020). Chinese Medical Association; Chinese Medical Doctor Association, Hematology BranchChinese Guidelines for the Clinical Application of Antibacterial Drugs for Agranulocytosis with Fever (2020). *Zhonghua Xue Ye Xue Za Zhi* 14, 41. doi:10.3760/cma.j.issn.0253-2727.2020.12.001

Dan-Li, L., Xi-Ying, S., L.Qiand Xiao-Jia, W. (2015). Progress in Prevention and Treatment of Chemotherapy Induced Febrile Neutropenia in Patients with Breast Cancer. *China Cancer* 24, 9. doi:10.11735/j.issn.1004-0242.09.A015

Donadieu, J., Fenneteau, O., Beaupain, B., Mahlaoui, N., and Chantelot, C. B. (2011). Congenital Neutropenia: Diagnosis, Molecular Bases and Patient Management. *Orphanet J. Rare Dis.* 6, 26. doi:10.1186/1750-1172-6-26

Esteva, F. J., Valero, V., Pusztai, L., Boehnke-Michaud, L., Buzdar, A. U., and Hortobagyi, G. N. (2001). Chemotherapy of Metastatic Breast Cancer: what to Expect in 2001 and beyond. *Oncologist* 6, 133–146. doi:10.1634/theoncologist.6-2-133

Gao, L., and Li, S. C. (2018). Cost-effectiveness Analysis of Lipegfilgrastim as Primary Prophylaxis in Women with Breast Cancer in Australia: a Modelled Economic Evaluation. *Breast Cancer* 25, 671–680. doi:10.1007/s12282-018-0872-6

Garcia-Carbonero, R., Mayordomo, J. I., Tornamira, M. V., Lopez-Brea, M., Rueda, A., Guillem, V., et al. (2001). Granulocyte colony-stimulating Factor in the Treatment of High-Risk Febrile Neutropenia: a Multicenter Randomized Trial. *JNCI J. Natl. Cancer Inst.* 93, 31–38. doi:10.1093/jnci/93.1.31

Huang, L., Mei, Z., Wu, Z., Zeng, X., and Yan, P. (2021). A Systematic Review on Efficacy and Safety of Mecapegfilgrastim as Prophylaxis for

Chemotherapy-induced Neutropenia. *J. Pract. Med.* 37, 6. doi:10.3969/j.issn.1006-5725.2021.06.020

Huang, W., Liu, J., Zeng, Y., Wu, F., Li, N., Chen, K., et al. (2018). Randomized Controlled Clinical Trial of Polyethylene Glycol Recombinant Human Granulocyte colony-stimulating Factor in the Treatment of Neutropenia after Chemotherapy for Breast Cancer. *Cancer Chemother. Pharmacol.* 82, 607–613. doi:10.1007/s00280-018-3639-z

Jiang, Z. F., Xu, F. R., Fan, J., Li, B. J., Gao, J. N., Hu, J. W., et al. (2018). A Multicenter, Randomized, Controlled, Phase Ⅳ Clinical Study of PEG-rhG-CSF for Preventing Chemotherapy Induced Neutropenia in Patients with Breast Cancer. *Zhonghua Yi Xue Za Zhi* 98, 1231–1235. doi:10.3760/cma.j.issn.0376-2491.2018.16.009

Knudsen, E., Iversen, P. O., Bøyum, A., Seierstad, T., Nicolaysen, G., and Benestad, H. B. (2011). G-CSF Enhances the Proliferation and Mobilization, but Not the Maturation Rate, of Murine Myeloid Cells. *Eur. J. Haematol.* 87, 302–311. doi:10.1111/j.1600-0609.2011.01658.x

Kuderer, N. M., Dale, D. C., Crawford, J., and Lyman, G. H. (2007). Impact of Primary Prophylaxis with Granulocyte colony-stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: a Systematic Review. *J. Clin. Oncol.* 25, 3158–3167. doi:10.1200/JCO.2006.08.8823

Lapidari, P., Gbenou, A., Havas, J., Martin, E., Pistilli, B., Martin, A. L., et al. (2021). Long-term Patient Reported Outcomes and Hematologic Toxicity Among Patients Who Received Granulocyte-Colony Stimulating Factors during Chemotherapy for Early Breast Cancer. *Breast* 57, 43–48. doi:10.1016/j.breast.2021.02.014

Lathia, N., Isogai, P. K., De Angelis, C., Smith, T. J., Cheung, M., Mittmann, N., et al. (2013). Cost-effectiveness of Filgrastim and Pegfilgrastim as Primary Prophylaxis against Febrile Neutropenia in Lymphoma Patients. *J. Natl. Cancer Inst.* 105, 1078–1085. doi:10.1093/jnci/djt182

Li-Tian, J., Cong-Ling, G., Bin-Bin, C., and Chang-Sheng, F. (2019). Cost-effectiveness Analysis of Thiopentyl and Recombinant Human Granulocyte Stimulating Factor in Preventing Decrease of Related Neutropenia in Chemotherapy in Breast Cancer Patients. *China J. Pharm. Econ.* 14, 10. doi:10.12010/j.issn.1673-5846.10.003

Liu, G. G. (2020). *China Guidelines for Pharmacoeconomic Evaluations*. 2020 Edition. Beijing: China Market Press.

Liu, K. Q., Wang, Y., Zhao, Z., Lin, D., Zhou, C. L., Liu, B. C., et al. (2019). A single-center, Randomized Controlled Trial of PEG-rhG-CSF and Common rhG-CSF to Promote Neutrophil Recovery after Induction Chemotherapy in Newly Diagnosed Acute Myeloid Leukemia. *Zhonghua Xue Ye Xue Za Zhi* 40, 497–501. doi:10.3760/cma.j.issn.0253-2727.2019.06.009

Liverani, C., Mercatali, L., Spadazzi, C., La Manna, F., De Vita, A., Riva, N., et al. (2014). CSF-1 Blockade Impairs Breast Cancer Osteoclastogenic Potential in Co-culture Systems. *Bone* 66, 214–222. doi:10.1016/j.bone.2014.06.017

Ma, J., Cao, M., Yao, Y., Zou, F., Li, Y., and Yu, H. (2020). Efficacy of Long or Short Recombinant Human Granulocyte colony Stimulating Factor on Malignant Tumor Patients under Multi-cycle Chemotherapy. *J. Pract. Med.* 36, 20. doi:10.3969/j.issn.1006-5725.2020.20.014

Mhaskar, R., Clark, O. A., Lyman, G., Engel Ayer Botrel, T., Morganti Paladini, L., and Djulbegovic, B. (2014). Colony-stimulating Factors for Chemotherapy-Induced Febrile Neutropenia. *Cochrane Database Syst. Rev.* 30, CD003039. doi:10.1002/14651858.CD003039.pub2

Ming, J., Wei, Y., Sun, H., Wong, G., Yang, G., Pong, R., et al. (2019). Cost-Effectiveness of Cryoballoon Ablation versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation in China: Results Based on Real-World Data. *Value Health* 22, 863–870. doi:10.1016/j.jval.2019.02.001

Peto, R., Peto, R., Davies, C., Godwin, J., Gray, R., Pan, H. C., et al. (2012). Comparisons between Different Polychemotherapy Regimens for Early Breast Cancer: Meta-Analyses of Long-Term Outcome Among 100,000 Women in 123 Randomised Trials. *Lancet* 379, 432–444. doi:10.1016/S0140-6736(11)61625-5

Sheng, Y., Xiaohui, H. E., Peng, L., Zhou, S., Mei, D., Yan, Q., et al. (2015). Efficacy Analysis of Pegylated Filgrastim as Prophylaxis for Chemotherapy-Induced Neutropenia. *Chin. J. Clin. Oncol.* 42, 12. doi:10.3969/j.issn.1000-8179.20150577

Wang, L., Baser, O., Kutikova, L., Page, J. H., and Barron, R. (2015). The Impact of Primary Prophylaxis with Granulocyte colony-stimulating Factors on Febrile Neutropenia during Chemotherapy: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Support Care Cancer* 23, 3131–3140. doi:10.1007/s00520-015-2686-9

Wong, G., Zhang, L., Majeed, H., Razvi, Y., DeAngelis, C., Lam, E., et al. (2020). A Retrospective Review of the Real-World Experience of the Pegfilgrastim Biosimilar (Lapelga®) to the Reference Biologic (Neulasta®). *J. Oncol. Pharm. Pract.* 28, 1–5. doi:10.1177/1078155220974085

World Health Organization (2020). World Cancer Report: Cancer Research for Cancer Prevention. Available at: https://www.iarc.who.int/cards_page/world-cancer-report/(Accessed February 4, 2020).

Xia, W., Wang, S. S., Hu, H., Zhao, F. L., Xu, F., Hong, R. X., et al. (2020). Cost-effectiveness of Primary Prophylaxis with PEG-rhG-CSF in Early-Stage Breast Cancer Patients Receiving Chemotherapy in China. *Zhonghua Zhong Liu Za Zhi* 42, 861–867. doi:10.3760/cma.j.cn112152-20200616-00565

Xie, J., Cao, J., Wang, J. F., Zhang, B. H., Zeng, X. H., Zheng, H., et al. (2018). Advantages with Prophylactic PEG-rhG-CSF versus rhG-CSF in Breast Cancer Patients Receiving Multiple Cycles of Myelosuppressive Chemotherapy: an Open-Label, Randomized, Multicenter Phase III Study. *Breast Cancer Res. Treat.* 168, 389–399. doi:10.1007/s10549-017-4609-6

Zhang, J. Y., Liu, Y. X., Wang, H., Mi, L., Song, G. H., Jiang, H. F., et al. (2018). The Role of Prophylactic Use of Pegylated Recombinant Human Granulocyte colony-stimulating factor(PEG-rhG-CSF) in Breast Cancer Receiving Adjuvant Chemotherapy. *Zhonghua Yi Xue Za Zhi* 98, 2718–2721. doi:10.3760/cma.j.issn.0376-2491.2018.34.008

Zhang, W., Wang, Y., Ding, N., Liu, X., Wang, C., Zhai, J., et al. (2018). Efficacy and Cost-Effectiveness Analysis of Long or Short Recombinant Human Granulocyte Stimulating Factor on Malignant Tumor Patients with Leucopenia. *Anti-tumor Pharm.* 8, 5. doi:10.3969/j.issn.2095-1264.2018.05.36

Zhang, Y.-N., Bao-xia, H., Zhang, Z.-X., Chen, J.-H., and Zhang, W.-Z. (2020). Cost-effectiveness Analysis of Short and Long Effective Granulocyte Stimulating Factor in Bone Marrow Suppression Induced by Chemotherapy for Malignant Tumors. *Chin. J. Hosp. Pharm.* 40, 20. doi:10.13286/j.1001-5213.2020.20.11

Zhu, J., Li, H., Fan, Z., Gao, Y., Tu, M., Shao, B., et al. (2019). Efficacy and Safety of PEG-rhG-CSF in Primary and Secondary Prevention of Chemotherapy-Induced Neutropenia. *Jco* 37, e19051. doi:10.1200/JCO.2019.37.15_suppl.e19051

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Clinical Outcome and Medical Cost of Originator and Generic Antihypertensive Drugs: A Population-Based Study in Yinzhou, China

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Background: The substitution of generic drugs can effectively alleviate the rapid growth of drug costs; however, the clinical effectiveness and medical costs of originator products and generics were barely studied in China.

Objectives: To compare the effectiveness of antihypertensive drugs and hypertension-related medical costs between originator and generic initiators in Yinzhou, China.

Methods: We conducted a population-based retrospective cohort study using the Chinese Electronic Health Records Research in Yinzhou (CHERRY), from July 1, 2011, to December 31, 2018. Hypertension patients initiating with originator products were compared with patients initiating with generic counterparts. We used 1:1 propensity score matching to pair the two groups based on sociodemographic, clinical, and health service utilization variables. Cox proportional regression was adopted to compare the rate of hospitalization for hypertension-related cardiovascular disease between matched originator and generic initiators. Wilcoxon matched-pairs signed-rank test was used to compare annual hypertension-related medical costs.

Results: Matched pairs (10,535) of patients were included in the comparative study of originator products and generics, corresponding to seven antihypertensive drugs including amlodipine, felodipine, nifedipine, irbesartan, losartan, valsartan, and metoprolol. The average age of patients included in the analysis was around 60 years (originator *vs*. generics initiators: from 59.0 *vs*. 59.1 years in losartan to 62.9 *vs*. 63.6 years in nifedipine). Higher hospitalization rates among originator initiators were observed for three calcium

Abbreviations: ARB, angiotensin receptor blockers; CVD, cardiovascular diseases; CCI, the Charlson comorbidity index; CCB, the calcium channel blockers; CHF, congestive heart failure; CHERRY, the Chinese Electronic Health Records Research in Yinzhou; CI, confidence interval; ED, emergency department; HR, hazard ratio; ICD-10, International Classification of Diseases Tenth Revision; INN, international nonproprietary name; IQR, interquartile range; MI, myocardial infarction; NMPA, the National Medical Products Administration; NSAID, nonsteroidal anti-inflammatory drug; SMD, standardized mean difference; UEBMI, the basic medical insurance for urban employees; URBMI, the basic medical insurance for urban residents.

channel blockers (hazard ratio[95% CI]: amlodipine, 3.18[1.43, 7.11]; felodipine, 3.60 [1.63, 7.98]; and nifedipine, 3.86[1.26, 11.81]; respectively). The remaining four out of seven drugs of the clinical endpoint estimates showed comparable outcomes between originator products and generics (hazard ratio[95% CI]: irbesartan, 1.19[0.50, 2.84]; losartan, 1.84[0.84, 4.07]; valsartan, 2.04[0.72, 5.78]; and metoprolol, 1.25[0.56, 2.80]; respectively). Higher median annual hypertension-related medical costs were observed in originator initiators (all $p < 0.001$), except for metoprolol ($p = 0.646$).

Conclusion: We observed comparable or even better clinical outcomes and less medical cost associated with the use of antihypertensive generics compared to originator counterparts. This could help increase patient and provider confidence in the efficacy of generic medicines to manage hypertension diseases.

Keywords: clinical outcome, generic, comparative effectiveness research, antihypertenisve, originator

INTRODUCTION

Increasing drug cost has emerged as a critical public health issue, straining the financial budgets of patients and contributing to poor medication adherence or treatment discontinuation (Su et al., 2017; Husain et al., 2020). Originator products sold at high prices have been a major contributor to elevated drug costs (Haas et al., 2005; Kesselheim et al., 2008). Thus, many countries, including the United States, Canada, the Netherlands, and some other European countries (Shrank et al., 2010; Godman et al., 2014; Mishuk et al., 2020; Godman et al., 2021), promoted substituting originators with less expensive generic drugs to control health expenditures and improve medication adherence (Shrank et al., 2006; WHO, 2010; Dylst and Simoens, 2011; Godman et al., 2014; Godman et al., 2021).

Generics are approved based on evidence of pharmaceutical equivalence and bioequivalence with originator drugs. Several systematic reviews and meta-analyses have compared the clinical characteristics of generics and originator products used for cardiovascular diseases (CVD) and showed no superiority of the latter over the former. Nonetheless, heterogeneities remained between studies, and most studies included were bioequivalence trials (Kesselheim et al., 2008; Manzoli et al., 2016; Leclerc et al., 2020). Although several observational studies have investigated the clinical equivalence of generics to originator products, they demonstrated ambiguous results (Kesselheim et al., 2008; Manzoli et al., 2016; Desai et al., 2019; Leclerc et al., 2020). Given a lack of real-world evidence, many patients still perceived generics as less clinically effective and safe with the belief that being cheap implied being inferior (Babar et al., 2011; Ngo et al., 2013; Dunne and Dunne, 2015; Toverud et al., 2015).

In China, the government has implemented a series of health policies to encourage the research and development of generics to promote market competition and reduce drug costs. However, bioequivalence studies are optional in the approval of generics in China. A lack of bioequivalence results in undermining the confidence of both health professionals and patients in the clinical effectiveness of generics, contributing to a relatively low prescribing rate of generics in China (Zeng, 2013; Huang et al., 2017; Jiang et al., 2020). Therefore, a better understanding of the comparative effectiveness of generics and their originator counterparts is urgently needed. Using a population-based data of Yinzhou, this study aimed to compare the clinical outcome and hypertension-related medical costs between patients initiating originator and generic antihypertensive drugs and to contribute to the evidence for better clinical decision-making.

MATERIALS AND METHODS

Study Design and Data Source

We conducted a population-based retrospective cohort study using the Chinese Electronic Health Records Research in Yinzhou (CHERRY) from July 1, 2011, to December 31, 2018.

The CHERRY was a relational database, including different administrative databases of sociodemographic characteristics, health check and death surveillance data, patient electronic medical records, and health insurance information. Since 2009, the CHERRY has covered 98% of permanent residents (about 1.24 million) in Yinzhou, Ningbo, Zhejiang. Details about the database could be found in previous studies (Lin et al., 2018; Yang et al., 2018). We extracted the following variables from the database in this study: 1) patient sociodemographic characteristics including sex, age, and insurance type; 2) prescription data including drug trade name, international nonproprietary name (INN), drug code (Anatomical Therapeutic Chemical Classification of Medications, ATC code), prescription date, and usage; 3) patient clinical information including diagnosis names, diagnosis type, diagnosis code (International Classification of Diseases, Tenth Revision, and ICD-10 code) and diagnosis date; and 4) patient death date from health check and death surveillance database.

Study Population and Follow-Up

We included patients aged ≥18 years who were diagnosed with hypertension (ICD-10 code: I10-I15) between July 1, 2011, and December 31, 2018, in the CHERRY database. The first antihypertensive drug prescription of each patient was identified as the index prescription, and the corresponding

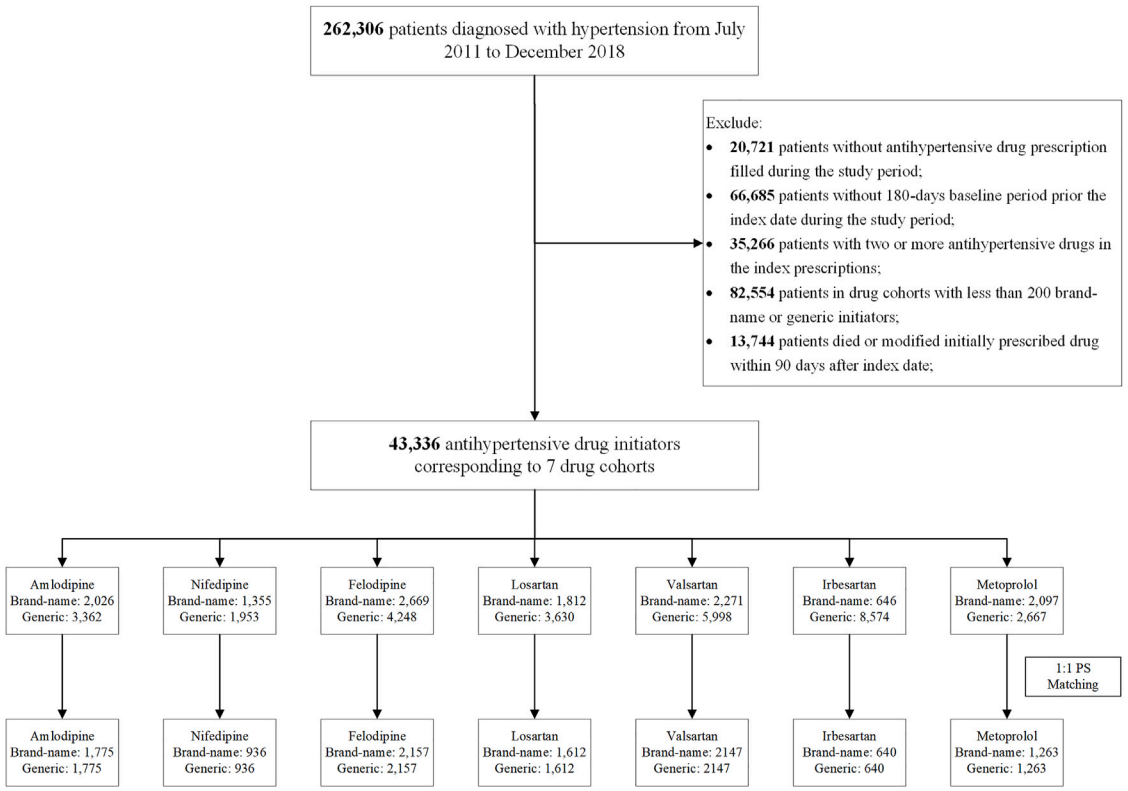

FIGURE 1 | Flow of sample selection.

date was regarded as the index date. We used 90 days for the induction period (minimal time needed between drug initiation and disease occurrence) and 0 days for the latent period (maximal time between drug modification and disease occurrence) (Lund et al., 2015). All patients included were followed from index date until the occurrence of the following events, whichever came first: 1) primary outcome, defined as hospitalization with hypertension-related CVD; 2) treatment discontinuation, defined as over 90 days lag time following the last dispensing; 3) treatment modification, including adding or transferring to another antihypertensive drug, 4) treatment switch, defined as switching from generics to originator counterparts or vice versa according to the originator manufacturer information on the National Medical Products Administration (NMPA) website (National Medical Products Administration, 2020); 5) death; and 6) end of the study (December 31, 2018).

We excluded the following: 1) patients without antihypertensive drug (details of drug information are in **Supplementary Table S1**) prescription filled during the study period; 2) patients without 180-day baseline period prior to the index date during the study period; 3) patients who initiated two or more antihypertensive drugs in the index prescription; and 4) patients who died or modified their initial antihypertensive drugs within 90 days after the index date (**Figure 1**).

Then we divided the patients into different study cohorts according to the INNs of their initially prescribed antihypertension drugs (e.g., amlodipine cohort, losartan cohort). In each drug cohort, patients were subsequently classified into either originator or generic initiators based on the originator manufacturer information from NMPA website (National Medical Products Administration, 2020). To obtain sufficient observed outcome events, we excluded patients with less than 200 originators or generic initiators (**Figure 1**).

Outcomes

The primary outcome was hospitalization with hypertension-related CVD, identified by the primary discharge diagnosis of patients (ICD-10 code I00-I25, I27-I88, and I95-I99) (Lewington et al., 2016).

The annual hypertension-related medical cost [in renminbi (RMB)] for each patient was calculated as total hypertension-related medical cost of outpatient visits during the follow-up period, including medication costs and examination costs (identified by the outpatient diagnosis (ICD-10 code: I10-I15), divided by the number of followed years.

Covariates

The main independent variable of interest was the generic or originator antihypertensive drug prescribed at the index date. Covariates were measured during the 180-day baseline period, including the following: 1) sociodemographic characteristics, including sex, age at the index date, and insurance type; 2) drug use information, comprising statins and other lipid lowering drugs, antiplatelets, insulin preparations, oral

hypoglycemic agents, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), nitrates, anticoagulants, digoxin, antiarrhythmics, and Coxibs (**Supplementary Table S2**); 3) health service utilization variables, containing all-cause outpatient visits, all-cause emergency department (ED) visits, and inpatient visits; and 4) the Charlson comorbidity index (CCI) score, estimated according to the baseline clinical information (Sundararajan et al., 2007).

Statistical Analysis

Within each drug cohort, propensity score was calculated by fitting a logistic regression model to predict the probability of initiating originator products *vs*. generics, as a function of the baseline covariates. A 1:1 propensity score matching using greedy nearest neighbor caliper matching without replacement was performed to balance the confounders between originator and generic initiators. A caliper width of 0.2 of the standard difference of the logit of the propensity score was used (Austin, 2011). Standardized mean differences (SMD) were used to estimate the differences of the covariates before and after matching between the two groups. A SMD <0.1 was considered to be statistically negligible (Normand et al., 2001).

In the matched cohort, the incidence rate was calculated, and the crude hazard ratio (HR) of hospitalization with hypertension-related CVD between originator *vs*. generic initiators was estimated by using Cox proportional hazard regression model with a robust sandwich-type variance estimator to account for the matched nature of the sample (Lin and Wei, 1989; Austin, 2013). Furthermore, the crude hazard ratio for treatment discontinuation, treatment switch, and treatment modification of originator *vs*. generic initiators were estimated. The proportional hazards assumption was assessed by the Schoenfeld residuals test. Annual hypertension-related medical costs were calculated and compared using either matched *t*-test or Wilcox matched-pairs signed-rank test between two groups.

All analyses were performed using the Stata (version 14.1). Ninety-five percent confidence interval (CI) and *p*-value were reported. A two-side *p*-value <0.05 was considered to be statistically significant.

Sensitive Analysis

We conducted the following sensitivity analyses to test the robustness of our results. First, subgroup analyses were performed to test the potential effect modification of age; patients without prior hospitalization; emergency visits in the baseline period; patients without prior diagnosed myocardial infarction (MI), stroke, or congestive heart failure (CHF) in the baseline period; and patients without treatment discontinuation within the early 180 days in the follow-up period, respectively. Second, as the mechanism for hypertension-inducing CVD is unclear, different induction and latent time intervals (0, 30, 60, and 90 days) were used to compare the results.

Ethics Statement

The research was granted ethical exemption by the Ethical Committee of Peking University (No.208027). Participants were not involved in the study design, data extraction, and analysis.

RESULTS

Patient Characteristics

A total of 43,336 hypertension patients were included in the comparisons of originator and generic initiators. After propensity score matching, 21,070 patients remained across seven drugs (amlodipine, felodipine, nifedipine, irbesartan, losartan, valsartan, and metoprolol) (**Figure 1**).

Baseline characteristics of patients in each drug cohort between originator and generic initiators were summarized in **Supplementary Tables S3–S9**. After propensity score matching, baseline variables were balanced between the two groups except index year of nifedipine and felodipine, and aspirin use in losartan. The study population aged around 60 years (originator *vs*. generics initiators: ranged from 59.0 *vs*. 59.1 years in losartan to 62.9 *vs*. 63.6 years in nifedipine). More patients were enrolled in the medical insurance for urban employees (UEBMI) or medical insurance for urban residents (URBMI) (originator *vs*. generic initiators: ranged from 65.1% *vs*. 63.8% in metoprolol to 93.6% *vs*. 92.2% in irbesartan). The average baseline CCI score was about 0.3 (originator *vs*. generic initiators: ranged from 0.28 *vs*. 0.25 in amlodipine to 0.40 *vs*. 0.45 in irbesartan).

Hospitalization for Hypertension-Related CVD

The median follow-up time for originator initiators ranged from 0.30[IQR:0.25, 0.77] years in metoprolol to 0.48[IQR: 0.25, 1.21] years in irbesartan and valsartan, and that of the generic initiators ranged from 0.44[IQR: 0.25, 1.04] years in metoprolol to 0.70 [IQR: 0.34, 1.47] years in irbesartan. Higher hospitalization rates in the originator initiators were observed for the three calcium channel blockers (CCB) (HR [95% CI]: amlodipine, 3.18[1.43, 7.11]; felodipine, 3.60[1.63, 7.98]; and nifedipine, 3.86[1.26, 11.81]; respectively) (**Table 1**). For angiotensin receptor blockers (ARBs) and beta-blockers, no significant differences were found in the hospitalization rates for hypertension-related CVD between originator initiators *vs*. generic initiators (HR [95% CI]: irbesartan, 1.19[0.50, 2.84]; losartan, 1.84[0.84, 4.07]; valsartan, 2.04[0.72, 5.78]; and metoprolol, 1.25[0.56, 2.80]; respectively) (**Table 1**).

Annual Hypertension-Related Medical Cost

The median annual hypertension costs for originator initiators ranged from RMB715.4 (interquartile range/IQR: 262.8, 1,529.4) for metoprolol to RMB1,595.1 (IQR: 814.0, 2,814.2) for losartan, while the median annual hypertension costs for generic initiators ranged from RMB419.8 (IQR: 171.6, 985.5) for nifedipine to RMB1,204.5 (IQR: 598.6, 2,182.7) for losartan. Higher median annual hypertension-related medical costs were observed in originator initiators ($p < 0.001$), except metoprolol ($p = 0.646$) (**Table 2**).

TABLE 1 | Hospitalization for hypertension-related CVD of originator *vs*. generic initiators after 1:1 propensity score matching.

Drug		Group	Sample size, n	Follow-up, median (IQR)/years	Total person-years	Hospitalization events, n	Hospitalization rate/ 1,000 person-years	HR (95% CI)
CCBs	Amlodipine	Originator	1,775	0.47 (0.25, 1.15)	1,640	23	14	3.18 (1.43, 7.11)
		Generic	1,775	0.61 (0.30, 1.34)	1,710	7	4.1	Reference
	Felodipine	Originator	2,157	0.38 (0.25, 0.95)	1,906	24	12.6	3.60 (1.63, 7.98)
		Generic	2,157	0.51 (0.25, 1.25)	2,171	9	4.15	Reference
	Nifedipine	Originator	936	0.38 (0.25, 0.92)	840	16	19	3.86 (1.26, 11.81)
		Generic	936	0.46 (0.25, 1.05)	786	4	6	Reference
ARBs	Irbesartan	Originator	645	0.48 (0.25, 1.21)	584	11	18.8	1.19 (0.50, 2.84)
		Generic	645	0.70 (0.34, 1.47)	643	7	10.9	Reference
	Losartan	Originator	1,612	0.43 (0.25, 0.96)	1,389	16	11.5	1.85 (0.84, 4.07)
		Generic	1,612	0.51 (0.25, 1.17)	1,468	11	7.5	Reference
	Valsartan	Originator	2,147	0.48 (0.25, 1.21)	2,060	10	4.9	2.04 (0.72, 5.78)
		Generic	2,147	0.62 (0.28, 1.38)	2,170	6	2.8	Reference
Beta-blocker	Metoprolol	Originator	1,263	0.30 (0.25, 0.77)	1,083	12	11.1	1.25 (0.56, 2.80)
		Generic	1,263	0.44 (0.25, 1.04)	1,138	11	9.7	Reference

Abbreviations: CVD, cardiovascular diseases; IQR, interquartile range; HR, hazard ratio; CI, confidence interval. CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

TABLE 2 | Annual hypertension-related medical cost for originator *vs*. generic initiators after 1:1 propensity score matching.

Drug		Group	Sample size, n (missing)[a]	Annual cost, median (IQR)/RMB	*p*-value
CCBs	Amlodipine	Originator	1,775 (166)	1,306.7 (631.5, 2,274.0)	<0.001
		Generic	1,775 (183)	759.2 (350.4, 1,449.1)	
	Felodipine	Originator	2,157 (102)	981.9 (459.9, 1,759.3)	<0.001
		Generic	2,157 (98)	569.4 (262.8, 1,109.6)	
	Nifedipine	Originator	936 (53)	1,259.3 (573.1, 2,332.4)	<0.001
		Generic	936 (41)	419.8 (171.6, 985.5)	
ARBs	Irbesartan	Originator	645 (70)	1,471.0 (704.5, 2,799.6)	<0.001
		Generic	645 (88)	835.9 (390.6, 1,686.3)	
	Losartan	Originator	1,612 (152)	1,595.1 (814.0, 2,814.2)	<0.001
		Generic	1,612 (93)	1,204.5 (598.6, 2,182.7)	
	Valsartan	Originator	2,147 (223)	1,416.2 (737.3, 2,430.9)	<0.001
		Generic	2,147 (128)	861.4 (438.0, 1,584.1)	
Beta-blocker	Metoprolol	Originator	1,263 (33)	704.5 (262.8, 1,529.4)	0.646
		Generic	1,263 (15)	741.0 (266.5, 1,646.2)	

[a]*Patients with missing cost data in the matched cohorts were excluded when comparing hypertension-related medical costs.*
Abbreviations: IQR, interquartile range; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

Treatment Discontinuation, Switch, and Modification

Higher treatment discontinuation rates were observed in originator initiators in six drugs (HR [95% CI]: amlodipine, 1.28[1.17, 1.39]; felodipine, 1.23[1.14, 1.32]; irbesartan, 1.20 [1.04, 1.39]; losartan, 1.31[1.20, 1.43]; valsartan, 1.09[1.01, 1.18]; and metoprolol, 1.29[1.18, 1.40]) except nifedipine (HR [95% CI]: 1.04[0.93, 1.15]) (**Table 3**). Originator initiators of irbesartan and losartan (HR [95% CI]: 5.50[2.07, 14.65] and 1.95 [1.22, 3.13], respectively) were more likely to switch their treatments compared to generic initiators (**Table 3**). Meanwhile, higher modification rate was observed in originator initiators of metoprolol (HR [95% CI]: 1.28[1.01, 1.60]), and lower modification rates were found in originator initiators of amlodipine and losartan (HR [95% CI]: 0.74[0.63, 0.86] and 0.76[0.64, 0.90], respectively) (**Table 3**).

Sensitivity Analysis

Results of subgroup analyses were similar to primary analysis (**Supplementary Figure S1A** and **Supplementary Table S10–S12**). In the subgroup analysis of age, no significant differences were observed in the hospitalization rates between originator and generic group for nifedipine initiators aged <65 years and aged ≥65 years (HR [95% CI]: 4.61[0.96, 22.20]

TABLE 3 | Treatment discontinuation, switch, and modification of originator *vs.* generic initiators after 1:1 propensity score matching.

Drug		Group	Sample size, n	Total person-years	Treatment discontinuation			Treatment switch			Treatment modification		
					Events, n	IR/1,000 person-years	HR (95%CI)	Events, n	IR/1,000 person-years	HR (95%CI)	Events, n	IR/1,000 person-years	HR (95%CI)
CCBs	Amlodipine	Originator	1,775	1,640	956	582.9	1.28 (1.17, 1.39)	16	582.9	1.85 (0.84, 4.08)	284	173.2	0.74 (0.63, 0.86)
		Generic	1,775	1,710	801	468.4	Reference	10	468.4	Reference	436	255	Reference
	Felodipine	Originator	2,157	1,906	1,329	697.3	1.23 (1.14, 1.32)	49	697.3	1.25 (0.84, 1.86)	274	143.8	0.96 (0.82, 1.13)
		Generic	2,157	2,171	1,184	545.4	Reference	48	545.4	Reference	349	160.8	Reference
	Nifedipine	Originator	936	840	551	656	1.04 (0.93, 1.15)	12	656	1.98 (0.76, 5.12)	120	142.9	0.94 (0.73, 1.20)
		Generic	936	786	546	694.7	Reference	6	694.7	Reference	133	169.2	Reference
ARBs	Irbesartan	Originator	645	581	332	571.4	1.20 (1.04, 1.39)	23	571.4	5.50 (2.07, 14.65)	104	179	1.00 (0.77, 1.31)
		Generic	645	621	304	489.5	Reference	5	489.5	Reference	124	199.7	Reference
	Losartan	Originator	1,612	1,389	974	701.2	1.31 (1.20, 1.43)	46	701.2	1.95 (1.22, 3.13)	208	149.7	0.76 (0.64, 0.90)
		Generic	1,612	1,468	794	540.9	Reference	27	540.9	Reference	315	214.6	Reference
	Valsartan	Originator	2,147	2,060	1,135	551	1.09 (1.01, 1.18)	39	551	0.97 (0.63, 1.50)	392	190.3	1.01 (0.88, 1.16)
		Generic	2,147	2,170	1,116	514.3	Reference	46	514.3	Reference	432	199.1	Reference
Beta-blocker	Metoprolol	Originator	1,263	1,073	865	806.2	1.29 (1.18, 1.40)	21	806.2	0.86 (0.49, 1.52)	150	139.8	1.28 (1.01, 1.60)
		Generic	1,263	1,122	743	662.2	Reference	31	662.2	Reference	142	126.6	Reference

Abbreviations: IR, incidence ratio; HR, hazard ratio; CI, confidence interval. CCB, calcium channel blocker; ARB, angiotensin receptor blocker

and 3.18[0.89, 11.30], respectively), and felodipine initiators aged <65 years (HR [95% CI]: 1.03[0.34, 3.10]). A significantly higher hospitalization rate was found in the originator group for metoprolol initiators aged ≥65 years (HR [95% CI]: 4.62[1.34, 15.96]) (**Supplementary Figure S1**). For patients without treatment discontinuation within 180 days in the follow-up, no significant difference was observed in originator and generic initiators of nifedipine (HR [95% CI]: 1.89[0.78, 4.61]), and significantly higher hospitalization rates were founded in originator initiators of irbesartan and losartan (HR [95% CI]: 2.57[1.39, 4.74] and 3.85[1.30, 11.39], respectively) (**Supplementary Table S10**).

As induction time became shorter, higher estimated hazard ratios of hospitalization were observed between originator and generic initiators of irbesartan, losartan, and valsartan (Supplemenatary Table S11). Meanwhile, given different induction and latent time, significantly higher hypertension-related costs for originator initiators were found as in prior analysis (**Supplementary Table S12**).

DISCUSSION

Our findings indicated comparable or even better clinical effectiveness and lower hypertension-related medical costs in generic antihypertensive drug initiators compared with those in originator initiators. As the first study to compare the clinical outcomes and medical costs of originator and generic drugs in China, we provided critical evidence for generic substitution and clinical practice.

Consistent with most studies on generics and the pooled result of random controlled trials, our study found comparable clinical outcomes of generics and originator products for hospital visits (Desai et al., 2019; Gagne et al., 2014; Gagne et al., 2015). Noticeably, we found lower hospitalization rates for CVD in generic initiators for three CCB drugs out of the seven drug cohorts, which could be attributable to different levels of medication adherence in the two patient groups. In this study, generic initiators were less likely to discontinue their treatment compared with originator initiators. This finding echoed previous studies in which patients treated with generics experienced better clinical outcomes (Corrao et al., 2014; Gagne et al., 2014).

Besides, we found substantially lower medical costs in generic initiators, indicating the potential of generic substitution to save drug costs. Hypertension was the primary risk factor for cardiovascular disease, a leading cause of mortality in China (Lewington et al., 2016). As originator antihypertensive drugs implied a significant financial commitment, only 23% of hypertension patients in China regularly took originator antihypertensive drugs, and less than 16% had effective blood pressure control (Ho et al., 2009; Lu et al., 2017; Su et al., 2017). Besides, higher cost may negatively impact patient adherence to medicines and thus clinical outcomes (Sinnott et al., 2013; Mann et al., 2014; Simoens and Sinnaeve, 2014; Banerjee et al., 2016). Given the comparable clinical effectiveness of generics, patients and healthcare providers can be reassured to preferentially use generics to lower drug costs and improve medication adherence

and ultimately blood pressure control rate. Therefore, we suggest Chinese regulators to promote generics use and establish relevant health policies of generic substitution (Shrank et al., 2010; Mishuk et al., 2020).

Our study had several strengths. Compared with prior observational studies, we balanced potential confounding through propensity score matching, which was used in only a few previous studies and made our results more robust and reliable (Leclerc et al., 2020). Besides, we required a 180-day antihypertensive drug-naive period before treatment initiation and considered the incubation and latent time; these designs further controlled for unmeasured confounding factors, such as hypertension history and the dose modification at the beginning of follow-up.

However, our study also had several limitations. First, we included drug use information and CCI score in the baseline period to balance baseline clinical characteristics of patients between originator and generic treatment groups. Nevertheless, blood pressure, body mass index, and other variables were missing from the data, making it difficult to fully capture the health status of individual patients. Second, we failed to obtain all patients' income information in the dataset. Previous studies demonstrated that high-income patients tended to use originator products and be hospitalized for mild symptoms (Zhao et al., 2019), probably leading to higher hospitalization rates (Vrijens et al., 2012). However, we included 18,118 patients with income information in the additional analysis and found a non-significant impact of income on initiating originator products or generics (**Supplementary Table S13**). Furthermore, given that whether the patients chose to be hospitalized could be influenced by the severity of diseases and income, we adopted hospitalization for MI, stroke, and CHF as the secondary outcome (Lin et al., 2018), and the results suggested our primary analysis result remained valid (**Supplementary Figure S2**). Third, we did not distinguish between generic products of the same INN from different manufactures; thus, further studies need to investigate the clinical effectiveness of individual generics from different manufacturers. Fourth, we only included patients treated with monotherapy, which comprised 81.5% of all patients treated for hypertension (Lu et al., 2017). Patients in our study were thus likely to represent a cohort with mild hypertension, as most severe hypertension patients need two or more antihypertensive drugs to effectively control blood pressure according to the guidelines (Wang et al., 2020). Fifth, similar to previous studies (Corrao et al., 2008; Corrao et al., 2014; Desai et al., 2019), the follow-up period of sample patients was relatively short due to complicated endpoints, including treatment discontinuation, modification, and switching. Sixth, immortal time bias might have been introduced by excluding patients who died or modified treatment within the 90-day incubation period. Last, our population was limited to residents of Yinzhou, which is a district in Ningbo, an economically developed coastal city of southeast China. Thus, our findings should be extrapolated with caution.

CONCLUSION

We observed comparable or even better clinical outcomes and less medical cost associated with the antihypertensive generics compared with their originator counterparts. This could help increase health professional and patient confidence in the efficacy of generic medicines and promote the use of generics to manage hypertension.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Peking University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XG and LS conceptualized and designed the study. TH, MY, PS, HL, and ZW screened and completed data extractions and analyses. TH and XG contributed to interpreting the results. TH, XG, LB, and HW commented on the draft manuscripts. All authors refined the versions of and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.757398/full#supplementary-material

REFERENCES

Austin, P. C. (2011). Optimal Caliper Widths for Propensity-Score Matching when Estimating Differences in Means and Differences in Proportions in Observational Studies. *Pharm. Stat.* 10 (2), 150–161. doi:10.1002/pst.433

Austin, P. C. (2013). The Performance of Different Propensity Score Methods for Estimating Marginal hazard Ratios. *Stat. Med.* 32 (16), 2837–2849. doi:10.1002/sim.5705

Babar, Z. U., Grover, P., Stewart, J., Hogg, M., Short, L., Seo, H. G., et al. (2011). Evaluating Pharmacists' Views, Knowledge, and Perception Regarding Generic Medicines in New Zealand. *Res. Soc. Adm Pharm* 7 (3), 294–305. doi:10.1016/j.sapharm.2010.06.004

Banerjee, A., Khandelwal, S., Nambiar, L., Saxena, M., Peck, V., Moniruzzaman, M., et al. (2016). Health System Barriers and Facilitators to Medication Adherence for the Secondary Prevention of Cardiovascular Disease: a Systematic Review. *Open Heart* 3 (2), e000438. doi:10.1136/openhrt-2016-000438

Corrao, G., Soranna, D., La Vecchia, C., Catapano, A., Agabiti-Rosei, E., Gensini, G., et al. (2014). Medication Persistence and the Use of Generic and Brand-Name Blood Pressure-Lowering Agents. *J. Hypertens.* 32 (5), 1146–1153. doi:10.1097/HJH.0000000000000130

Corrao, G., Zambon, A., Parodi, A., Poluzzi, E., Baldi, I., Merlino, L., et al. (2008). Discontinuation of and Changes in Drug Therapy for Hypertension Among Newly-Treated Patients: a Population-Based Study in Italy. *J. Hypertens.* 26 (4), 819–824. doi:10.1097/HJH.0b013e3282f4edd7

Desai, R. J., Sarpatwari, A., Dejene, S., Khan, N. F., Lii, J., Rogers, J. R., et al. (2019). Comparative Effectiveness of Generic and Brand-Name Medication Use: A Database Study of US Health Insurance Claims. *Plos Med.* 16 (3), e1002763. doi:10.1371/journal.pmed.1002763

Dunne, S. S., and Dunne, C. P. (2015). What Do People Really Think of Generic Medicines? A Systematic Review and Critical Appraisal of Literature on Stakeholder Perceptions of Generic Drugs. *BMC Med.* 13, 173. doi:10.1186/s12916-015-0415-3

Dylst, P., and Simoens, S. (2011). Does the Market Share of Generic Medicines Influence the price Level?: a European Analysis. *Pharmacoeconomics* 29 (10), 875–882. doi:10.2165/11585970-000000000-00000

Gagne, J. J., Choudhry, N. K., Kesselheim, A. S., Polinski, J. M., Hutchins, D., Matlin, O. S., et al. (2014). Comparative Effectiveness of Generic and Brand-Name Statins on Patient Outcomes: a Cohort Study. *Ann. Intern. Med.* 161 (6), 400–407. doi:10.7326/M13-2942

Gagne, J. J., Kesselheim, A. S., Choudhry, N. K., Polinski, J. M., Hutchins, D., Matlin, O. S., et al. (2015). Comparative Effectiveness of Generic versus Brand-Name Antiepileptic Medications. *Epilepsy Behav.* 52 (Pt A), 14–18. doi:10.1016/j.yebeh.2015.08.014

Godman, B., Fadare, J., Kwon, H. Y., Dias, C. Z., Kurdi, A., Dias Godói, I. P., et al. (2021). Evidence-based Public Policy Making for Medicines across Countries: Findings and Implications for the Future. *J. Comp. Eff. Res.* 10 (12), 1019–1052. doi:10.2217/cer-2020-0273

Godman, B., Wettermark, B., van Woerkom, M., Fraeyman, J., Alvarez-Madrazo, S., Berg, C., et al. (2014). Multiple Policies to Enhance Prescribing Efficiency for Established Medicines in Europe with a Particular Focus on Demand-Side Measures: Findings and Future Implications. *Front. Pharmacol.* 5, 106. doi:10.3389/fphar.2014.00106

Haas, J. S., Phillips, K. A., Gerstenberger, E. P., and Seger, A. C. (2005). Potential Savings from Substituting Generic Drugs for Brand-Name Drugs: Medical Expenditure Panel Survey, 1997-2000. *Ann. Intern. Med.* 142 (11), 891–897. doi:10.7326/0003-4819-142-11-200506070-00006

Ho, P. M., Bryson, C. L., and Rumsfeld, J. S. (2009). Medication Adherence: its Importance in Cardiovascular Outcomes. *Circulation* 119 (23), 3028–3035. doi:10.1161/CIRCULATIONAHA.108.768986

Huang, B., Barber, S. L., Xu, M., and Cheng, S. (2017). Make up a Missed Lesson-New Policy to Ensure the Interchangeability of Generic Drugs in China. *Pharmacol. Res. Perspect.* 5 (3), e00318. doi:10.1002/prp2.318

Husain, M. J., Datta, B. K., Kostova, D., Joseph, K. T., Asma, S., Richter, P., et al. (2020). Access to Cardiovascular Disease and Hypertension Medicines in Developing Countries: An Analysis of Essential Medicine Lists, Price, Availability, and Affordability. *J. Am. Heart Assoc.* 9 (9), e015302. doi:10.1161/JAHA.119.015302

Jiang, B., Wang, H., Zhou, L., Shi, L., and Nie, Y. (2020). Pharmacists' Perceptions of Generic Drugs in China. *J. Chin. Pharm. Sci.* 29 (5), 364–368.

Kesselheim, A. S., Misono, A. S., Lee, J. L., Stedman, M. R., Brookhart, M. A., Choudhry, N. K., et al. (2008). Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: a Systematic Review and Meta-Analysis. *Jama* 300 (21), 2514–2526. doi:10.1001/jama.2008.758

Leclerc, J., Thibault, M., Midiani Gonella, J., Beaudoin, C., and Sampalis, J. (2020). Are Generic Drugs Used in Cardiology as Effective and Safe as Their Brand-Name Counterparts? A Systematic Review and Meta-Analysis. *Drugs* 80 (7), 697–710. doi:10.1007/s40265-020-01296-x

Lewington, S., Lacey, B., Clarke, R., Guo, Y., Kong, X. L., Yang, L., et al. (2016). The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China. *JAMA Intern. Med.* 176 (4), 524–532. doi:10.1001/jamainternmed.2016.0190

Lin, D. Y., and Wei, L. J. (1989). The Robust Inference for the Cox Proportional Hazards Model. *J. Am. Stat. Assoc.* 84 (408), 1074–1078. doi:10.1080/01621459.1989.10478874

Lin, H., Tang, X., Shen, P., Zhang, D., Wu, J., Zhang, J., et al. (2018). Using Big Data to Improve Cardiovascular Care and Outcomes in China: a Protocol for the Chinese Electronic Health Records Research in Yinzhou (CHERRY) Study. *BMJ Open* 8 (2), e019698. doi:10.1136/bmjopen-2017-019698

Lu, J., Lu, Y., Wang, X., Li, X., Linderman, G. C., Wu, C., et al. (2017). Prevalence, Awareness, Treatment, and Control of Hypertension in China: Data from 1·7 Million Adults in a Population-Based Screening Study (China PEACE Million Persons Project). *Lancet* 390 (10112), 2549–2558. doi:10.1016/S0140-6736(17)32478-9

Lund, J. L., Richardson, D. B., and Stürmer, T. (2015). The Active Comparator, New User Study Design in Pharmacoepidemiology: Historical Foundations and Contemporary Application. *Curr. Epidemiol. Rep.* 2 (4), 221–228. doi:10.1007/s40471-015-0053-5

Mann, B. S., Barnieh, L., Tang, K., Campbell, D. J., Clement, F., Hemmelgarn, B., et al. (2014). Association between Drug Insurance Cost Sharing Strategies and Outcomes in Patients with Chronic Diseases: a Systematic Review. *PLoS One* 9 (3), e89168. doi:10.1371/journal.pone.0089168

Manzoli, L., Flacco, M. E., Boccia, S., D'Andrea, E., Panic, N., Marzuillo, C., et al. (2016). Generic versus Brand-Name Drugs Used in Cardiovascular Diseases. *Eur. J. Epidemiol.* 31 (4), 351–368. doi:10.1007/s10654-015-0104-8

Mishuk, A. U., Fasina, I., and Qian, J. (2020). Impact of U.S. Federal and State Generic Drug Policies on Drug Use, Spending, and Patient Outcomes: A Systematic Review. *Res. Soc. Adm Pharm* 16 (6), 736–745. doi:10.1016/j.sapharm.2019.08.031

National Medical Products Administration (2020). Data Query: National Medical Products Administration. [cited 2020 Mar 14]. Available from: http://app1.sfda.gov.cn/datasearchcnda/face3/dir.html?WxUg5ztDmi=1584176709193#maodian1.

Ngo, S. N., Stupans, I., and McKinnon, R. A. (2013). Generic Substitution in the Treatment of Epilepsy: Patient Attitudes and Perceptions. *Epilepsy Behav.* 26 (1), 64–66. doi:10.1016/j.yebeh.2012.10.032

Normand, S. T., Landrum, M. B., Guadagnoli, E., Ayanian, J. Z., Ryan, T. J., Cleary, P. D., et al. (2001). Validating Recommendations for Coronary Angiography Following Acute Myocardial Infarction in the Elderly: a Matched Analysis Using Propensity Scores. *J. Clin. Epidemiol.* 54 (4), 387–398. doi:10.1016/s0895-4356(00)00321-8

Shrank, W. H., Choudhry, N. K., Agnew-Blais, J., Federman, A. D., Liberman, J. N., Liu, J., et al. (2010). State Generic Substitution Laws Can Lower Drug Outlays under Medicaid. *Health Aff. (Millwood)* 29 (7), 1383–1390. doi:10.1377/hlthaff.2009.0424

Shrank, W. H., Hoang, T., Ettner, S. L., Glassman, P. A., Nair, K., DeLapp, D., et al. (2006). The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions. *Arch. Intern. Med.* 166 (3), 332–337. doi:10.1001/archinte.166.3.332

Simoens, S., and Sinnaeve, P. R. (2014). Patient Co-payment and Adherence to Statins: a Review and Case Studies. *Cardiovasc. Drugs Ther.* 28 (1), 99–109. doi:10.1007/s10557-013-6497-2

Sinnott, S. J., Buckley, C., O'Riordan, D., Bradley, C., and Whelton, H. (2013). The Effect of Copayments for Prescriptions on Adherence to Prescription Medicines in Publicly Insured Populations; a Systematic Review and Meta-Analysis. *PLoS One* 8 (5), e64914. doi:10.1371/journal.pone.0064914

Su, M., Zhang, Q., Bai, X., Wu, C., Li, Y., Mossialos, E., et al. (2017). Availability, Cost, and Prescription Patterns of Antihypertensive Medications in Primary Health Care in China: a Nationwide Cross-Sectional Survey. *Lancet* 390 (10112), 2559–2568. doi:10.1016/S0140-6736(17)32476-5

Sundararajan, V., Quan, H., Halfon, P., Fushimi, K., Luthi, J. C., Burnand, B., et al. (2007). Cross-national Comparative Performance of Three Versions of the ICD-10 Charlson index. *Med. Care* 45 (12), 1210–1215. doi:10.1097/MLR.0b013e3181484347

Toverud, E. L., Hartmann, K., and Håkonsen, H. (2015). A Systematic Review of Physicians' and Pharmacists' Perspectives on Generic Drug Use: What Are the Global Challenges? *Appl. Health Econ. Health Pol.* 13 Suppl 1 (Suppl. 1Suppl 1), S35–S45. doi:10.1007/s40258-014-0145-2

Vrijens, F., Van de Voorde, C., Farfan-Portet, M. I., and Vander Stichele, R. (2012). Patient Socioeconomic Determinants for the Choice of the Cheapest Molecule within a Cluster: Evidence from Belgian Prescription Data. *Eur. J. Health Econ.* 13 (3), 315–325. doi:10.1007/s10198-011-0367-2

Wang, J. G., Chia, Y. C., Chen, C. H., Park, S., Hoshide, S., Tomitani, N., et al. (2020). What Is New in the 2018 Chinese Hypertension Guideline and the Implication for the Management of Hypertension in Asia? *J. Clin. Hypertens. (Greenwich)* 22 (3), 363–368. doi:10.1111/jch.13803

Who (2010). *Cost Savings of Switching Private Sector Consumption from Originator Brands to Generic Equivalents*. Geneva: World Health Organization.

Yang, Y., Zhou, X., Gao, S., Lin, H., Xie, Y., Feng, Y., et al. (2018). Evaluation of Electronic Healthcare Databases for Post-Marketing Drug Safety Surveillance and Pharmacoepidemiology in China. *Drug Saf.* 41 (1), 125–137. doi:10.1007/s40264-017-0589-z

Zeng, W. (2013). A price and Use Comparison of Generic versus Originator Cardiovascular Medicines: a Hospital Study in Chongqing, China. *BMC Health Serv. Res.* 13 (1), 390. doi:10.1186/1472-6963-13-390

Zhao, Y., Mahal, A. S., Haregu, T. N., Katar, A., Oldenburg, B., and Zhang, L. (2019). Trends and Inequalities in the Health Care and Hypertension Outcomes in China, 2011 to 2015. *Int. J. Environ. Res. Public Health* 16 (22), 4578. doi:10.3390/ijerph16224578

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