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Biomarkers and early warning scores: The time for high-precision emergency medicine

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Biomarkers and early warning scores: The time for high-precision emergency medicine

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Editorial: Biomarkers and early warning scores: the time for high-precision emergency medicine

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Editorial on the Research Topic
Biomarkers and early warning scores: the time for high-precision emergency medicine

The research field of emergency medicine is a broader area that generally entails several diseases. In addition, the complexity is even greater considering that clinical practice can be performed inside the hospital, by emergency departments (ED), or out-of-hospital, by emergency medical services (EMS). A critical factor commonly faced by the whole range of professionals that constitute the emergency medicine field is the early identification of patients at risk of clinical deterioration. Briefly, those professionals must confront time-dependent decisions under limited information, and sometimes with limited resources, with life-threatening conditions.

Actually, there are biomarker and early warning scores (EWS), designed to provide more information regarding the patient status. Both have shown their utility to determine the clinical impairment of patients. The aim of this Research Topic was to shed light on the biomarker and EWS used in emergency medicine, and includes brief research reports, original research, reviews, and systematics reviews.

Due to the huge number of conditions faced in emergency field, the different works presented in this Research Topic deal with the prediction of a wide range of diseases: infection Risk prediction by using machine learning-based techniques (Feng T. et al.), COVID-19 (Fu et al.; Xiao et al.; Nogueira et al.; Wang et al.; Roy-Vallejo et al.), poisoning (Yu et al.), trauma alone (Li et al.) or trauma complicated with sepsis (Feng K. et al.), acute aortic dissection (Chen et al.), cerebrovascular diseases (Deguchi et al.), and neurological patients (Donoso-Calero et al.). There were also studies describing biomarkers not for particular diseases,

but for all patients admitted to the ICU (Tang et al.). In the collection presented here, other elements have also been studied, such as the assessment of overcrowding in emergency departments, which also influences the quality of care, the weekday or season showed to be important for the ED workload (Hitzek et al.). In this sense, previous triage by phone (Katayama et al.) could help to improve the always oversaturated ED. Or even, the proposal of one of the studies, in which the authors describe the utility of using a syndromic surveillance after a catastrophic event (Fernandez et al.).

As the different studies in this Research Topic shown, there are several EWS. Therefore, a key question arises: which of them is the most valuable? This was answered, at least for the prehospital setting, by one of the studies. The authors presented a systematic review that concludes that National Early warning Score (NEWS) is the most suitable for out-of-hospital (Burgos-Esteban et al.). Another work performed a critical review of the different predicting models that exist in the context of COVID-19 pandemic (Botz et al.).

To conclude, both EWS and biomarkers are a reality in the field of emergency medicine. They are tools under continuous development and research. However, many of them are already fully integrated in decision making, which due to its complexity, must take into account all the available evidence. Finally, the variety of topics covered in this collection demonstrates the great complexity and difficulty involved in this health specialty.

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Influence of Weekday and Seasonal Trends on Urgency and In-hospital Mortality of Emergency Department Patients

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Background: Given the scarcity of resources, the increasing use of emergency departments (ED) represents a major challenge for the care of emergency patients. Current health policy interventions focus on restructuring emergency care with the help of patient re-direction into outpatient treatment structures. A precise analysis of ED utilization, taking into account treatment urgency, is essential for demand-oriented adjustments of emergency care structures.

Methods: Temporal and seasonal trends in the use of EDs were investigated, considering treatment urgency and hospital mortality. Secondary data of 287,119 ED visits between 2015 and 2017 of the two EDs of Charité Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow Klinikum were analyzed.

Result: EDs were used significantly more frequently on weekends than on weekdays (Mdn = 290 vs. 245 visits/day; $p < 0.001$). The proportion of less urgent, outpatient emergency visits on weekends was above average. Holiday periods were characterized by at least 6, and at most 176 additional ED visits. In a comparison of different holidays, most ED visits were observed at New Year (+68% above average). In addition, a significant increase in in-hospital mortality on holidays was evident among inpatients admitted to hospital *via* the ED (3.0 vs. 3.2%; $p < 0.001$), with New Year's Day being particularly striking (5.4%).

Conclusion: These results suggest that, in particular, the resource planning of outpatient emergency treatment capacities on weekends and holidays should be adapted to the increased volume of non-urgent visits in EDs. Nevertheless, treatment capacities for the care of urgent, inpatient emergencies should not be disregarded and further research projects are necessary to investigate the causes of increased mortality during holiday periods.

Keywords: utilization (U), emergency department (ED), seasonal trends, temporal trends, urgency, hospital mortality, secondary data analysis

INTRODUCTION

The increasing use of emergency departments (ED) poses a major challenge for the care of emergency patients. In comparison with other countries who are part of the Organization for Economic Co-operation and Development (OECD), Germany has an average annual growth rate of 4.9% in the use of ED visits that result in inpatient treatment. This is significantly above the average (2.4%) of other OECD countries and thus Germany shows the fourth highest growth rate (1). Furthermore, Berlin is the federal state with the highest number of outpatient ED visits, although this number has been declining modestly since 2016 (2–4). The causes for the increasing case numbers might be limited resources of other health care providers (i.e., long waiting times to specialist treatment or elective procedures), but effects of demographic change with increasing numbers of older patients with complex medical and nursing needs are also reported (1, 5). Another factor might be changes in society's attitude toward standards and expectations of comprehensive medical treatment at the highest technical and scientific level, as well as the day-to-day availability of EDs, which seem to lead to a preferred usage of EDs by younger patients with less urgent conditions (6, 7). In addition, structural problems of the outpatient emergency care system and patients' lack of knowledge of treatment alternatives by statutory health insurance (SHI)-accredited physicians are associated with increasing case numbers in EDs (5, 7–9). Emergency care in Germany is provided by three independent sectors, which are organized on a federal basis. The outpatient treatment by physicians in private practice and the on-call service of the Association of Statutory Health Insurance Physicians (SHI), the rescue service, and inpatient care by the emergency departments (10). For adequate emergency treatment in the ED, the availability of room and personnel capacities, diagnostic equipment and, above all, patient number in relation to these resources are decisive for the quality and efficiency of care processes. A reduction in the quality of medical care and effects on medical outcomes, e.g., mortality, have already been demonstrated in studies on ED-crowding (7, 11, 12). Next to the shortage of specialists and the reduction of hospital beds, the increased use of emergency departments by patients, requiring less urgent care, has been identified as a trigger for crowding (7, 11, 12). In addition, negative effects on care and mortality have been discussed in the context of hospital admission on weekends, known as the "weekend-effect (13). An examination of weekday and temporal and seasonal trends in the use of ED with regards to treatment urgency thus provides important insights for a more efficient planning of available resources and alternative treatment options.

In the present study, temporal and seasonal trends of ED utilization with special regard to treatment urgency were examined in secondary data of two urban, tertiary care EDs of the Charité–Universitätsmedizin Berlin over a period of 3 years.

MATERIALS AND METHODS

The study included secondary data of 287,119 emergency visits in the EDs of the Charité-Universitätsmedizin Berlin, Germany, Campus Mitte (CCM) and Campus Virchow-Klinikum (CVK) between 2015 and 2017. These are two emergency rooms, of maximum-care hospitals and located in the inner-city area of Berlin. The CCM ED is an interdisciplinary ED with an attached emergency ward. Emergency care at CVK, on the other hand, is organized into three independent EDs. These include a surgical ED, an internal ED with an attached emergency ward, and the pediatric ED. Patients in the pediatric ED and patients who visited one of the EDs due to an accident at work were not included in the analyses.

Data

As part of the analysis, data collected and stored for quality assurance purposes from the EDs of CCM and CVK were used. In this context, data sets from 2015 to 2017 were extracted electronically from the hospital information system and converted into a table format. Subsequently, the data set was compressed to the aspects relevant to the research question before the data set was transferred to the statistics program SPSS for data preparation and subsequent analysis. Taking into account the underlying research interest, the case level was defined as the unit of analysis. In case that patients visited the ED several times during the study period, the different visits were considered as a separate case in the analysis. This offers the possibility to show a differentiated picture of the actual use of ED.

In the medical context, the term "season" is associated with a higher incidence of certain diseases within a certain period of time, for example, seasonal fluctuations in infectious diseases (14). There is currently no generally valid definition of seasonality in the medical context. In the current study, "seasonal trends" were defined as "cyclical fluctuations that repeat at regular intervals and do not exceed a period of 1 year": seasons, month, school vacation, and holidays (15). "Temporal trends" were defined as daily fluctuations with reference to the time of day. In-hospital mortality analyses was defined as the event of death either in the ED or during subsequent inpatient stay. Other variables considered in the analyses, as well as their operationalization presented in **Table 1**. All Data were managed and analyzed using IBM SPPS Statistics V25. Quantitative characteristics were described by median (Mdn), first (Q1) and third quartile (Q3) and maxima and minima. Qualitative variables were described by relative and absolute frequencies. Before performing adequate statistical tests, a visual test for normal distribution was performed using histograms for the variables "number of cases per day" and "age". In addition to the visual test, the Kolmogorov-Smirnov and Shapiro-Wilk tests were also used to check for normal distribution. For group comparisons the Chi-square test was used for categorical variables and due to skewed distributions Kruskal Wallis tests were performed for quantitative variables. A p-value of $p < 0.05$ was considered as significant. Due to the descriptive, exploratory nature of this work, no corrections for multiple testing were performed. The effect of holidays, weekends, school vacations and seasons on ED utilization were analysed by multiple linear regression. Outliers were analyzed and defined by the IQR method of Tukey. The interquartile range (IQR) was calculated

TABLE 1 | Definition and Operationalization of variables included in analyses.

Variables	Description	
Variables with seasonal reference		
Seasons	Spring, Summer, Autumn, Winter (astronomical classification)	
Month	January, February, March, April, May, June, July, August, September, October, November, December	
School vacations Berlin/Brandenburg	Winter holidays	02.02.–07.02.2015/01.02.–06.02.2016 31.01.–04.02.2017
	Easter holidays	30.03.–11.04.2015/21.03.–02.04.2016 10.04.–22.04.2017
	Whitsun holidays	26.05.2015/17.05.–18.05.2016 06.06.–09.06.2017
	Summer holidays	16.07.–28.08.2015/21.07.–03.09.2016 20.07.–01.09.2017
	Autumn holidays	19.10.–31.10.2015/17.10 –28.10.2016 23.10.–04.11.2017
	Christmas holidays	01.01.–02.01.2015/23.12.–03.01.2017 21.12.–31.12.2017
	Single day holidays	15.05.2015/06.05.2016/24.05.2017 26.05.2017 /02.10.2017
Day of the week	Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday	
Holidays	New Year	01.01.2015/16/17
	Good Friday	03.04.2015/25.03.2026/14.04.2017
	Easter Sunday	05.04.2015/27.03.2016/16.04.2017
	Easter Monday	06.04.2015/28.03.2016 /17.04.2017
	Ascension Day	14.05.2015/05.05.2016 /25.05.2017
	Labor Day	01.05.2015/16/17
	Whit Sunday	24.05.2015/15.05.2016/04.06.2017
	Whit Monday	25.05.2015/16.05.2016/05.06.2017
	German Unification Day	03.10.2015/16/17
	Reformation Day	31.10.2015/16/17
	Christmas Eve	24.12.2015/16/17
	Christmas Day	25.12.2015/16/17
	Christmas Day	26.12.2025/16/17
	27 December	
	New Year's Eve	31.12.2015/16/17
Variables with time reference		
Hours	0–23	
Outcome		
Emergency visits	Number of emergency visits	
Dimensions of stratification		
Age/sex	0–114/ men, women	
Urgency of treatment	Less urgent	category 4–5 (MTS)*
	Urgent	category 1–3 (MTS)*
Case type	Outpatient, inpatient	
Inpatient mortality	Proportion of patients deceased in hospital	

**MTS category describes the urgency of treatment using the Manchester triage system.*

by the difference of the third and first quartile (25 and 75 percentiles). We investigated outliers for two different scenarios; 1.5 times the IQR and 3 times the IQR. To compute the lower and upper border of the IQR we subtracted this value form the first quartile and added this value to the third quartile. All residuals with higher or lower values of the calculated 1.5x IQR and 3x IQR were defined as outliers.

The research project was approved by the institutional review board (EA1/082/18) and the institutional data protection department with reference to §24 and §25 LKG Berlin. Neither patients nor the public were involved in the design, or conduct, or dissemination plans of this research. The dataset generated and analyzed during the current study are available from the corresponding author (Jennifer Hitzek) on reasonable request.

RESULTS

The study population consisted of 142,954 visits of men (49.8%) and 144,151 visits of women (50.2%), for 14 participants gender was documented as unknown. The mean age was 40 (Mdn) years [28;60]. On average, 258 (Mdn) visits attended the EDs per day [238;284], with a minimum of 161 visits and a maximum of 439 visits per day.

Seasonal Trends

Spring was the season with the highest ED utilization with an average of Mdn = 269 visits per day [250;295]. The fewest visits were registered in autumn, averaging Mdn = 247 visits per day [231;273] (**Table 2**). With regard to monthly changes, March (Mdn = 259,[239;285]), April (Mdn = 267, [248;298]), May (Mdn = 278, [255;297]), June (Mdn = 266, [240;284]), July (Mdn = 266,[250;291]), August (Mdn = 259, [241;282]) and December (Med = 264, [238;294]) showed above-average patient numbers (**Figure 1A**; $p < 0.001$), while the months of January (Mdn = 246, [229;276]), February (Mdn = 250, [233;281]), September (Mdn = 244, [229;277]), October (Mdn = 251, [233;276]) and November (Mdn = 243, [238; 294]) showed a below-average utilization.

Temporal Trends

While the weekdays Tuesday to Thursday were rather under-average, an increase in the number of visits could be shown from Friday onwards, with Saturday being the day with the highest use of the EDs with an average increase of 17.8% as compared to the average ED visits (46 visits more per day) (**Figure 1B**). On Sundays, the average use was 9.0% higher as compared to the average ED visits (23 visits more per day) (**Table 2**).

Looking at the daily curve (**Figure 2A**), a steady increase in the use of EDs from 6:00 a.m. onwards, culminating in the first peak between 10 a.m. and 12 p.m. was found. Afterwards the number of patients in the ED decreased slightly, before another peak occurred between 3 and 5 p.m. An upstream peak on Monday (10 a.m.) was noticeable. On Fridays, however, the peak was shifted to the afternoon (4–5 p.m.).

ED Utilization During School Vacations and Holidays

In general, EDs were used more frequently during School vacations compared to days outside these periods (Mdn = 265, [246;292] 2 vs. Mdn = 255, [236;282] visits, $p < 0.001$, **Table 2**). If the annual average use of 258 (Mdn) visits per day [238;284] was taken as a reference, all other School vacations except the autumn and winter holidays showed above-average use of EDs (**Table 3**). The highest utilization was observed on single day holidays (Mdn = 305, [268;284] and during the Christmas holidays (Mdn = 300, [272;329]).

EDs were used more frequently on holidays than on non-holidays and in comparison to the annual average (Mdn = 303, [288;319] vs. Mdn = 255, [237;281] vs. Mdn = 258, [238;284] visits per day, $p < 0.001$, **Table 2**). New Year was characterized by the highest utilization with an average of 154 more visits per day (increase by 68.0%) and a total maximum of 439 visits per day (**Figure 1C**). On Whit Sunday the increase was 29.0% (77 visits more per day). In contrast to weekdays, ED were increasingly visited in the morning on weekends and holidays (9 a.m. - 1 p.m.). The second peak in ED utilization on weekdays in the afternoon was also not evident here; instead, utilization of ED decreased continuously from 2:00 p.m. onward (**Figure 2C**).

Stratification by Age, Gender, Urgency of Treatment, Inpatient Stay and Hospital Mortality

Age and Gender Specific ED Utilization

Emergency patients on weekends were on average 4 years younger than patients on weekdays (Mdn = 38, [27;56] vs. Mdn = 42, [28;61]; $p < 0.001$).

The daytime curve showed a gender-specific trend: During the day (10–20 o'clock), more women visited the ED, whereas at night (21–09 o'clock) more men used the ED (**Figure 2B**).

Clinical Characteristics in ED Patients

Fifty two percent of the visits were assigned to an urgent treatment category and 43.2% to a less urgent treatment category (**Figure 3**). The proportion of urgent visits was particularly high between 8 p.m. and 7 a.m. (>55.0%), whereas between 8 a.m. and 7 p.m. treatment urgency was on average (**Figure 2D**). The ratio of treatment urgency within the weekdays showed clear differences (**Table 2**): on Monday to Thursday more urgent visits predominated while on Fridays to Sundays the proportion of less urgent visits increased (**Figure 3**). Similarly, the proportion of urgent visits was lower on all school vacations than on non-vacations (48.9 vs. 55.0%). On 9 of 15 holidays, the proportion of less urgent visits exceeded the proportion of urgent visits. Easter Sunday (57.7%), New Year's Eve (55%) and New Year's Day (54.9%) were characterized by a very high proportion of less urgent ED visits (**Table 4**).

On average, 74.5% of visits resulted in an outpatient treatment and 25.5% in an inpatient treatment, respectively. There were significant differences in the type of admission, both in the comparison of weekdays and holidays. There was a lower proportion of outpatient visits between Monday and Thursday and an increase in outpatient visits from Friday to Saturday (**Table 2**). Furthermore, the proportion of ED outpatient visits (79.6%) was above the overall average (74.5%) on all holidays and highest on Good Friday and Whit Sunday with 82.5% respectively (**Table 2**).

Hospital mortality among inpatients was 3.0%, with an average increase up to 3.2% during holidays (**Figure 4**). A particularly high in-hospital mortality was observed on New Year's Eve (5.4%), Christmas Day (5.2%), German Unification Day and Christmas Eve (4.7% each). Although there was no increase in average in-hospital mortality when comparing holidays, the Pentecost holidays were characterized by an increase in in-hospital mortality up to 4.2%. In a comparison of the seasons and days of the week (**Table 2**) only slight differences in in-hospital mortality could be observed.

TABLE 2 | Overview of emergency visits by season, day of the week and holiday in total and stratified by demographic characteristics, treatment urgency, case type and mortality in the years 2015962017 in the emergency departments of Charité - Universitätsmedizin Berlin (CKV,CCM).

		Utilization behavior		Demographics			Classification of treatment urgency		Case type		Inpatient mortality
		Number of ED visits, (Mdn,[Q1;Q3])	Min/Max	ED visits men absolute in (%)	ED visits women absolute in (%)	age in years, (Mdn, [Q1;Q3])	Proportion of less urgent treatment cases absolute in (%)	Proportion of urgent treatment cases absolute in (%)	Proportion of inpatient treatment cases absolute in (%)	Proportion of outpatient treatment cases absolute in (%)	Proportion of deceased absolute in (%)
Seasons	Spring	269, [250;295]	186/365	37,620 (49.9)	37,823 (50.1)	40, [28;59]	33,263 (46.2)	38,779 (53.8)	18,565 (24.6)	56,870 (75.4)	543 (2.9)
	Summer	258, [240;283]	161/337	36,475 (49.7)	36,858 (50.3)	39, [27;58]	32,100 (45.8)	37,943 (54.2)	18,538 (25.3)	54,787 (74.7)	544 (2.9)
	Autumn	247, [231;273]	189/343	33,945 (49.9)	34,051 (50.1)	41, [28;61]	27,958 (43.2)	36,765 (56.8)	18,155 (26.7)	49,829 (73.3)	528 (2.9)
	Winter	253, [235;287]	183/439	34,914 (49.6)	35,419 (50.4)	41, [28;60]	30,672 (45.7)	36,457 (54.3)	17,919 (25.5)	52,400 (74.5)	557 (3.1)
	p-value	$p < 0.001$		$p < 0.812$		$p < 0.001$		$p < 0.001$		$p < 0.001$	$p < 0.001$
Weekdays	Monday	260, [242;274]	201/341	20,421 (50.5)	19,983 (49.5)	42, [28;62]	16,635 (43.2)	21,871 (56.8)	11,724 (29.0)	28,670 (71.0)	344 (2.9)
	Tuesday	238, [227;251]	161/327	18,884 (50.5)	18,536 (49.5)	42, [28;62]	15,093 (42.4)	20,505 (57.6)	10,660 (28.5)	26,757 (71.5)	328 (3.1)
	Wednesday	243, [228;255]	187/325	18,958 (50.2)	18,813 (49.8)	42, [28;61]	15,223 (42.4)	20,720 (57.6)	10,320 (27.3)	27,444 (72.7)	338 (3.3)
	Thursday	236, [224;247]	172/434	18,900 (50.7)	18,368 (49.3)	42, [28;62]	14,967 (42.2)	20,498 (57.8)	10,467 (28.1)	26,791 (71.9)	293 (2.8)
	Friday	265, [249;283]	191/439	20,982 (49.8)	21,111 (50.1)	41, [28;60]	18,468 (46.1)	21,608 (53.9)	10,528 (25.0)	31,562 (75.0)	307 (2.9)
	Saturday	304, [289;317]	257/398	23,326 (48.7)	24,573 (51.3)	38, [27;56]	23,158 (50.5)	22,698 (49.5)	9,746 (20.3)	38,151 (79.7)	266 (2.7)
	Sunday	281, [266;296]	214/369	21,483 (48.5)	22,767 (51.4)	38, [27;56]	20,449 (48.1)	22,035 (51.9)	9,732 (22.0)	34,514 (78.0)	296 (3.0)
	p-value	$p < 0.001$		$p < 0.001$		$p < 0.001$		$p < 0.001$		$p < 0.001$	$p < 0.001$
Weekdays, Weekends, Holidays	Weekdays	245, [231;262]	161/398	93,858 (50.4)	92,474 (49.6)	42, [28;61]	76,220 (43.0)	101,060 (57.0)	51,958 (27.9)	134,342 (72.1)	1,556 (3.0)
	Weekends	290, [276;311]	214/398	42,261 (48.6)	44,724 (51.4)	38, [27;56]	41,010 (49.2)	42,408 (50.8)	18,413 (21.2)	68,563 (78.8)	525 (2.9)
	Holidays	303, [288;318]	210/439	6,835 (49.6)	6,953 (50.4)	39, [27;57]	6,763 (51.1)	6,467 (48.9)	2,806 (20.4)	10,981 (79.6)	91 (3.2)
	p-value	$p < 0.001$		$p < 0.001$		$p < 0.001$		$p < 0.001$		$p < 0.001$	$p < 0.001$
	Totals	**258, [238;284]**	**161/439**	**142,955 (49.8)**	**144,151 (50.2)**	**40, [28;60]**	**123,993 (43.2)**	**149,935 (52.2)**	**73,177 (25.5)**	**213,886 (74.5)**	**2,172 (3.0)**

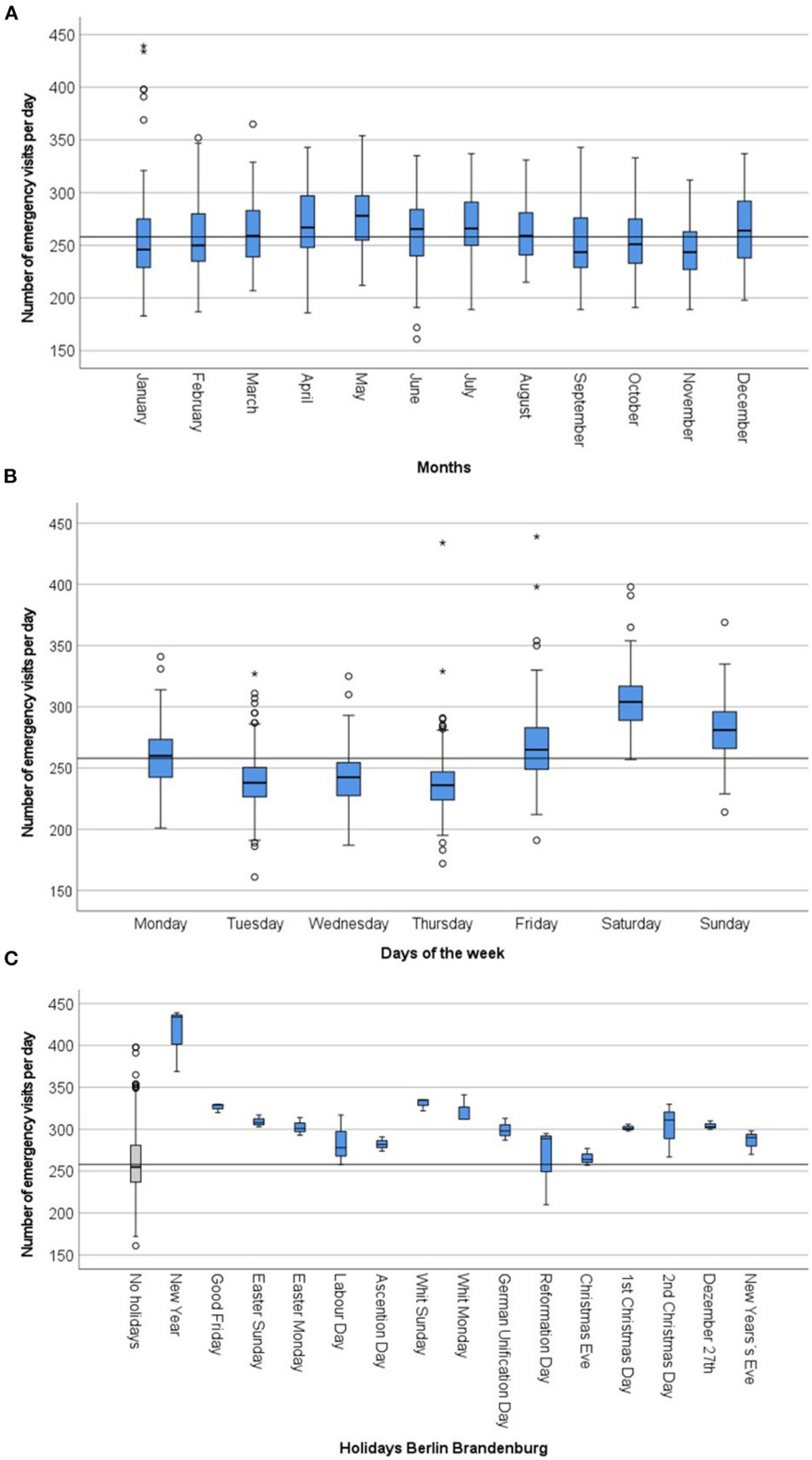

FIGURE 1 | Distribution of emergency visitis per day in comparison of months **(A)** in comparison of weekdays **(B)** and in comparison of holidays **(C)** in the years 2015-2017 in the emergency departments of Charité - Universitätsmedizin Berlin (CVK, CCM). The average daily use of emergency departments (median) in the study population serves as a reference line.

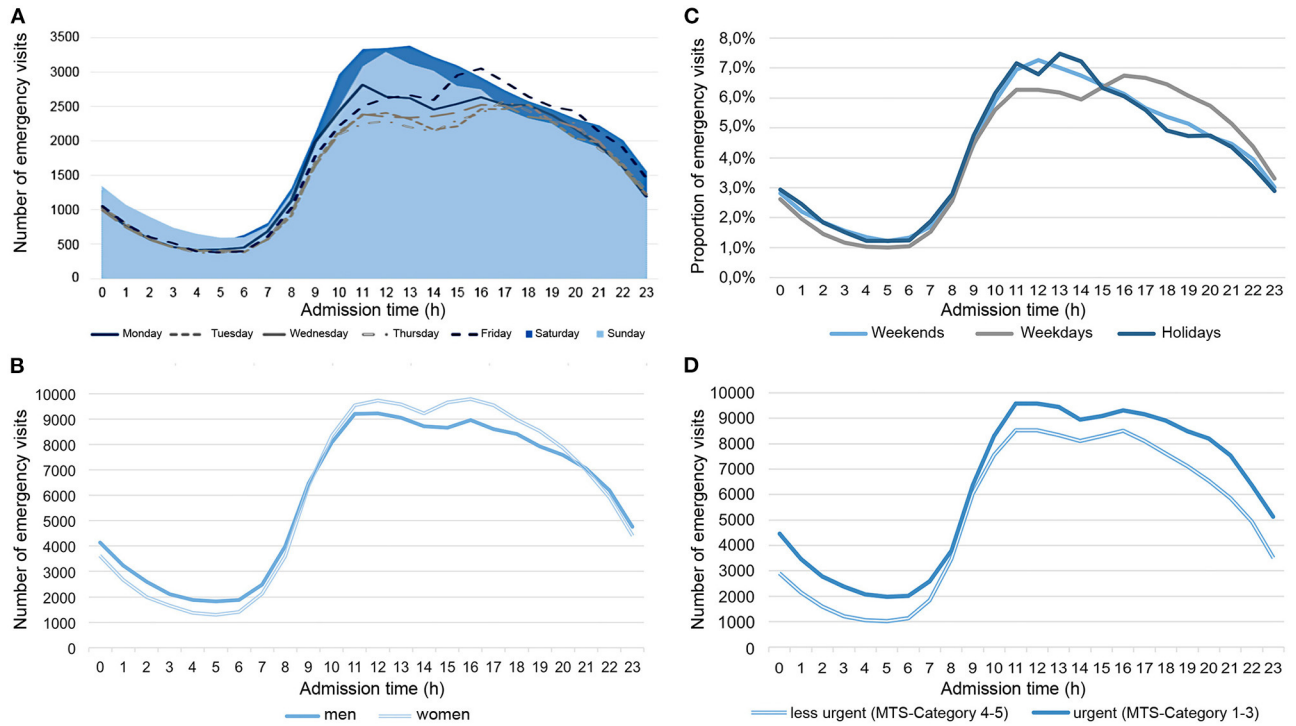

FIGURE 2 | Number of emergency visits depending on admission time in comparison of weekdays **(A)**, gender-specific differences **(B)**, in comparison of weekends, weekdays, holidays **(C)**, and the associated distribution of treatment urgency **(D)** in the years 2015–2017 in the emergency departments of Charité—Universitätsmedizin Berlin (CVK, CCM).

TABLE 3 | Average number of emergency visits compared to holidays in the years 2015 - 2017 in the emergency departments of Charité - Universitätsmedizin Berlin (CVK, CCM).

School vacations	Number of treatment cases	Median	IQR	Min.	Max.
Christmas holidays	11,118	300	272–329	233	439
Winter holidays	4,422	251	242–275	219	347
Easter holidays	11,147	281	254–315	233	365
Whitsun holidays	1,889	272	259–279	257	284
Summer holidays	35,076	259	241–283	215	337
Autumn holidays	9,521	248	236–265	206	311
Single day holidays	1,544	305	268–352	257	354
No holidays	212,402	255	236–282	161	398
Totals	287,119	258	238–284	161	439

Multifactorial Analysis of Effects Between ED Visits and Season, Weekend, Holidays and School Vacation

In the multifactorial linear regression model with the factors season, weekend, holiday and school vacation, a goodness of fit of 0.46 (adjusted R-squared) was achieved. A significant effect was found for all four factors (**Table 5**, $p < 0.001$). Weekends, holidays and school vacations were found to be factors with a positive effect i.e., increase in ED visits. Summer, autumn and winter, on the other hand, showed a negative effect compared to spring and were associated with a small decrease in ED visits. The predicted values of the model represented outliers in 2.4% (1.5x IQR) and 0.3% (3x IQR) of the cases (first quantile = −16, third quantile = 14). 0.9% of the 2.4% outliers were cases where the model overestimated the utilization of the ED and in 1.5% of the cases fewer ED visits were predicted than were actually observed. For the 3x IQR criterion 0.3% of the values deviated from the predicted model, with four outliers underestimated the actual utilization of the ED.

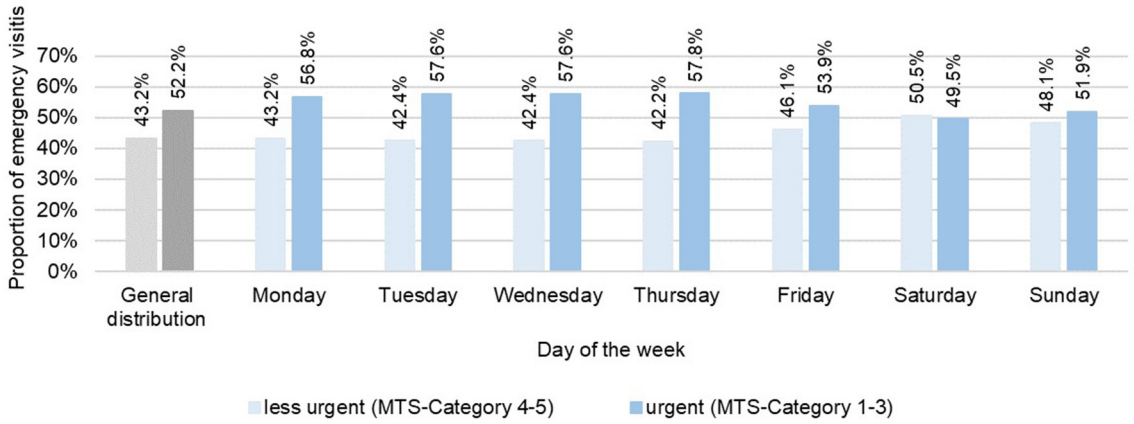

FIGURE 3 | Distribution of treatment urgency in the comparison of weekdays in the years 2015–2017 in the emergency departments of Charité—Universitätsmedizin Berlin (CVK, CCM).

TABLE 4 | Distribution of treatment urgency in comparison of holidays in the years 2015 - 2017 in the emergency departments of Charité - Universitätsmedizin Berlin (CVK, CCM).

	Treatment urgency less urgent		Treatment urgency urgent	
Holidays	**Number of emergency cases**	**Proportion in %**	**Number of emergency cases**	**Proportion in %**
New Year	443	54.9	530	45.1
Good Friday	483	51.2	460	048.8
Easter Sunday	521	57.7	382	42.3
Easter Monday	457	51.3	434	048.7
Ascension Day	437	52.8	391	47.2
Labour Day	370	45.7	439	054.3
Whit Sunday	456	48.8	478	51.2
Whit Monday	493	53.4	430	046.6
German Unification Day	423	49.1	439	50.9
Reformation Day	372	48.4	396	051.6
Christmas Eve	394	51.6	370	48.4
Christmas Day (25.12.)	434	49.4	445	050.6
Christmas Day (26.12.)	445	50.9	430	49.1
27 December	391	44.9	480	055.1
New Year's Eve	443	55.0	363	45.0
Totals	287,119	43.2		52.2

DISCUSSION

The current study examined relations between visits to ED at two German hospitals from 2015 to 2017 versus season, weekday, school vacation and holiday with stratification by five groups: age, sex, treatment urgency, case type (inpatient, outpatient), and in-hospital mortality. We found that weekends, school vacations and holidays are associated with an increased number of patients in the ED. The proportion of less urgent, outpatient emergency patients on these days is above average. The hospital mortality of inpatient emergency patients shows hardly any difference when comparing it with the days of the week, but it is above average on holidays and during the Whitsun holidays. Even though only a small number of patients visit the ED in autumn, these patients show the highest urgency of treatment and the highest proportion of inpatients regarding seasonal comparison. In the multifactorial linear regression model, a statistically significant influence could be demonstrated for the factors season, weekend, holidays and school vacation, independently of each other. Weekends and holidays are particularly associated with an increase in emergency department visits.

Aspects of Seasonal ED Utilization

The analyses of seasons and months could not prove a previously suspected decrease in the number of visits during the summer period. Autumn was characterized by the lowest utilization of EDs, while treatment urgency was higher during this period. Since processes might be prolonged in more urgent visits and treatment times in the ED might thus be longer, this could

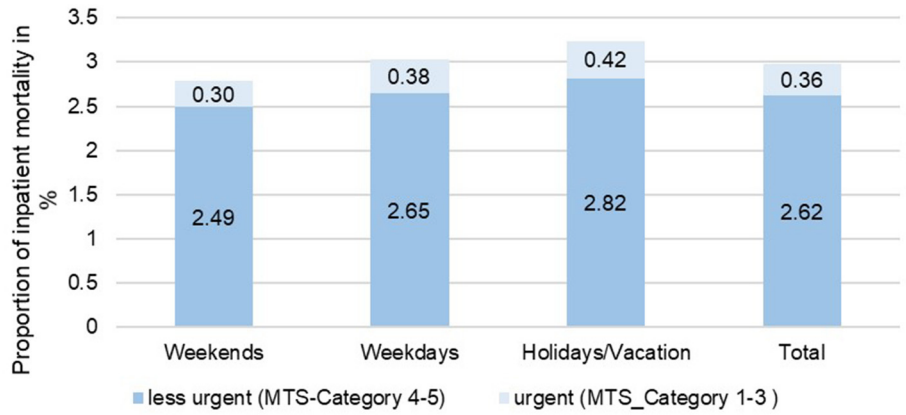

FIGURE 4 | Comparison of hospital mortality of inpatient treatment cases depending on the day of admission, taking into account the urgency of treatment in the years 2015–2017 in the emergency departments of Charité—Universitätsmedizin Berlin (CVK, CCM).

TABLE 5 | Multivariate effects of season, weekends, holidays and school vacations on number of ED visits in the years 2015–2017 in the emergency departments of Charité–Universitätsmedizin Berlin (CCM/CVK).

	Unstandardized coefficient B	95% Confidence interval for B	Significance
Constant (Number of ED visits)	257	(253, 260)	$p < 0.001$
Summer	−18	(−22, −13)	$p < 0.001$
Autumn	−21	(−25, −16)	$p < 0.001$
Winter	−11	(−15, −6)	$p < 0.001$
Weekend	45	(42, 48)	$p < 0.001$
Holidays	32	(25, 40)	$p < 0.001$
School vacations	14	(10, 17)	$p < 0.001$

1,096 days were investigated in this model. On average 262 (mean) visits attend the ED per day with a standard error of 1.04. A goodness of fit of 0.46 (adjusted R-square) was achieved and the residual standard error was 25.1.

be one explanation of the perceived crowding of EDs during autumn. These results implicate that the focus of personnel planning should not only be limited to case numbers, but also consider treatment urgency. A month-to-month comparison of the use of EDs showed an increase in April, May and July in particular. Fewer emergency patients visited the ED in January, February, September, October, and November. One possible explanation could be that recreational activities with a high risk of injury are performed more frequently during the months of higher utilization. Sports activities such as bicycling as well as the motorcycle season, are associated with an increased risk of injury, which could be reflected in the increased ED utilization during these months. The highest admission of accident patients to EDs in July has already been demonstrated in a study by Rising et al. (16). In addition, the period between April and July includes a large number of holidays, so that EDs are used more often than average, not only due to increased leisure activities, but also due to an increased number of tourists.

Holidays, School Vacations and Treatment Urgency

In the context of vacations, EDs offer a quick and low-barrier option for clarifying medical health problems. EDs are used particularly frequently during Christmas holidays and days off from school. The previous statements apply to the same extent for the days without school. The increase in the number of cases during the Christmas holidays is possibly due to the closing times of the outpatient health care system. A large number of general practitioners and specialists closed their practices during the Christmas period, so that the options for medical care are very limited. The increased use of EDs during holidays and on weekends, especially by non-urgent visits could partly be explained by closing times of the outpatient health care system and the lack of knowledge of the population about the outpatient emergency system by the Association of SHI-physicians (3–6). Further research is required to shed light in other causative factors for these observations. It is questionable but still possible that the results can partly be caused by an actual increase in medical emergencies. The increase of outpatient emergencies, up to over 80%, with less urgent treatment needs during holidays and on weekends is consistent with the results of other studies (3, 4, 17). This might be caused by the perceived need of rapid diagnostic clarification and treatment at the highest medical level of care by patients, which is likely to be taken for granted by patients in the ED (6, 8, 18). This advantage is particularly appealing for working people, since appointments in the outpatient care system, especially for specialist treatments, are sometimes associated with long waiting times or cannot be reconciled within working hours.

In-hospital Mortality and Weekend Effect

Taking into account the results on in-hospital mortality, an interesting area of conflict emerges: Although emergency patients are more likely to have a lower treatment urgency during holidays and the proportion of outpatients is higher (4, 19), in-hospital mortality of inpatients is increased during holidays. A reduction

in quality of medical care and a negative impact on outcomes such as mortality have already been demonstrated in the context of crowding in EDs (11, 12) and are underscored by the results presented in this paper. Internationally discussed negative effects on mortality at weekends could not be proven in the current analyses, this is in line with finding suggesting that the weekend effect is less pronounced in ED-patients (13). In fact, this may be a selection bias of university hospitals, as they are usually staffed 24/7 with specialist physicians in contrast to non-university hospitals. As a result, specialist treatment was available at all times in the investigated study population, so there are fewer delays in treatment and diagnosis than might be observed in other hospitals at weekends.

Aspects of Temporal ED Utilization and Practical Implications

The temporal trends regarding time of admission to the ED are in line with previous studies and might be helpful for planning of alternative resources (6, 20). In addition, the study shows gender-specific differences in the utilization behavior of ED patients. According to this, women primarily visit the ED during the day and at weekends, while the proportion of male emergency patients is higher at night. This could be explained, for example, by gender-specific disease incidences and their individual occurrence. Furthermore, it is possible that women visit the ED more often at times when they see tasks of family life secured by family support or institutional support. Regarding time of admission, two new aspects should be mentioned: (1) In addition to an earlier increase in the number of visits on Monday mornings, a subsequent increase in the afternoon on Fridays was seen. It could be hypothesized that these patients were referred to the ED by general practitioners or specialists at the beginning of the week for treatment or clarification of deteriorating general health or progressive developments of chronic diseases. The late shift in the number of visits on Fridays could be explained by the fact that patients prefer to go to the ED for rapid clarification of a medical health problem before the weekend (4). These effects might also be affected by the urban location of both EDs and need to be confirmed by multicenter analyses. (2) The results also show the increased need for more and experienced clinical personnel on weekends, which hospitals in some countries are not able to meet because of collective bargaining regulations (e.g., limited shits of weekends per month) and thus could be facilitated in cooperation with SHI-physicians. This is part of the current reform efforts for emergency care in Germany, which seem essential following the results shown in this study, showing an increased use of EDs at times when outpatient care is only available to a limited extent, especially by non-urgent patients with outpatient care needs (18, 21). The aim is not only to counteract the strong sectoral separation in the German health care system through closer cooperation between outpatient and hospital-based emergency care, through the establishment of integrated emergency centers, portal practices and networks of partner practices, but also to take into account the utilization behavior and treatment needs in emergency care when planning these structures.

LIMITATIONS

The analysis of secondary data is bound to some limitations, which must be critically reflected. The data quality of the evaluated data set was influenced by the documentation quality and documentation routine of the ED staff. The regular rotations of medical staff in the ED can lead to differences in documentation routine. Likewise, different medical specialties work in the ED with different documentation routines. Moreover, there are only few mandatory fields in the ED documentation and thus sometimes information is documented in free text fields or is only included in the physician's letter. Those data are not possible to extract for a high number of patients automatically. And last but not least another factor are the various documentation systems. In recent years, there have been many efforts to promote standardization in the documentation with slowly emerging success. Missing data occurred for gender in 0.2% of visits and for the urgency of treatment in 4.6% of visits. A high proportion of outpatient visits (74.5%) were not traced regarding mortality, but the mortality rate is expected to be low. For this reason, in-hospital mortality was determined on the basis of inpatient visits, which were completely available. In addition, the assessment of treatment urgency by MTS should be mentioned critically. The performance of the MTS by the responsible nursing staff depends on a variety of different factors, which may affect the assignment to treatment urgency levels. The assignment to the respective level of treatment urgency not only depends on the presenting leading symptom and symptom severity, it can be assumed that the utilization behavior itself has an impact on the classification of patients and thus influences the results for the assessment of treatment urgency.

Furthermore, there is currently no unique identifier for emergency treatment, thus a small proportion of patients called in for pre- or post-operative treatment in the ED might be included in the analyses (22–24). The representativeness of the sample is limited by the fact that both EDs are located in urban areas and are connected to hospitals providing maximum care. Further multi-center analyses should follow.

CONCLUSION

The current study examined temporal and seasonal trends in the use of EDs with respect to demographic characteristics, treatment urgency, case type (inpatient, outpatient), and in-hospital mortality according the emergency visits by season, day of the week and holidays. The peak ED demand occurs in weekends, in spring, on holidays and school vacations (ordered by the size of effect). Those are all periods of play when people are engaged in risky behavior. Thus, hospital administrators would be wise to have low levels of staffing when most people are at work or school, and high levels when they are mostly at play. Furthermore, these results suggest that, in particular, the resource planning of outpatient emergency treatment capacities on weekends and holidays should be adapted to the increased volume of non-urgent, outpatients visits in EDs during these periods. In addition to the utilization itself, treatment urgency and local patterns of utilization should also been considered

as factors in resource planning and health care measures. In particular the increased less urgent utilization at weekends and on public holidays, as well as on weekdays between 8 a.m. and 7 p.m. should be addressed by appropriate measures like increased clinical staff, on-call services by SHI-accredited doctors or additional GP services in the ED. The results of this study provide important indications for personnel and resource planning, as well as starting points for the further development of innovative, especially outpatient care structures and general practitioner cooperatives in emergency care in Germany. Based on the results, data on the urgency of patient treatment should be considered in addition to the pure case number consideration for appropriate personnel planning and the development of flanking outpatient services on weekends, school vacations and holidays. These measures could not only reduce the workload of medical staff, but also shorten waiting times for emergency patients and have a positive effect on the quality of treatment, also for more urgent cases whose outcome might be deteriorated by ED-crowding.

DATA AVAILABILITY STATEMENT

The dataset generated and analyzed during the current study is available from the corresponding author (Jennifer Hitzek) on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Charité—Universitätsmedizin Berlin. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JH, AS, AF-R, and MM were involved in the conception and design of the study, the acquisition, analysis and interpretation of data and approved the final version to be published, and are accountable for all aspects of the work. JH drafted the manuscript. JH and AS serve as guarantors for the manuscript. SK was involved in the interpretation of data, critically revised the manuscript for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Early Prediction Model for Critical Illness of Hospitalized COVID-19 Patients Based on Machine Learning Techniques

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Motivation: Patients with novel coronavirus disease 2019 (COVID-19) worsen into critical illness suddenly is a matter of great concern. Early identification and effective triaging of patients with a high risk of developing critical illness COVID-19 upon admission can aid in improving patient care, increasing the cure rate, and mitigating the burden on the medical care system. This study proposed and extended classical least absolute shrinkage and selection operator (LASSO) logistic regression to objectively identify clinical determination and risk factors for the early identification of patients at high risk of progression to critical illness at the time of hospital admission.

Methods: In this retrospective multicenter study, data of 1,929 patients with COVID-19 were assessed. The association between laboratory characteristics measured at admission and critical illness was screened with logistic regression. LASSO logistic regression was utilized to construct predictive models for estimating the risk that a patient with COVID-19 will develop a critical illness.

Results: The development cohort consisted of 1,363 patients with COVID-19 with 133 (9.7%) patients developing the critical illness. Univariate logistic regression analysis revealed 28 variables were prognosis factors for critical illness COVID-19 ($p < 0.05$). Elevated CK-MB, neutrophils, PCT, α-HBDH, D-dimer, LDH, glucose, PT, APTT, RDW (SD and CV), fibrinogen, and AST were predictors for the early identification of patients at high risk of progression to critical illness. Lymphopenia, a low rate of basophils, eosinophils, thrombopenia, red blood cell, hematocrit, hemoglobin concentration, blood platelet count, and decreased levels of K, Na, albumin, albumin to globulin ratio, and uric acid were clinical determinations associated with the development of critical illness at the time of hospital admission. The risk score accurately predicted critical illness in the development cohort [area under the curve (AUC) = 0.83, 95% CI: 0.78–0.86], also in the external validation cohort ($n = 566$, AUC = 0.84).

Conclusion: A risk prediction model based on laboratory findings of patients with COVID-19 was developed for the early identification of patients at high risk of progression to critical illness. This cohort study identified 28 indicators associated with critical illness of patients with COVID-19. The risk model might contribute to the treatment of critical illness disease as early as possible and allow for optimized use of medical resources.

Keywords: COVID-19, risk factors, critical illness, machine learning, LASSO regression

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is spreading worldwide. As a communicable disease, COVID-19 is caused by severe acute respiratory syndrome coronavirus 2. Until 14 February 2022, the WHO reported 412,044,520 COVID-19 confirmed cases globally, with an average mortality rate of 1.4%. The clinical spectrum of COVID-19 infection ranges from asymptomatic infection, and mild upper respiratory tract illness to critically ill cases (1). It has been reported that about 5% of patients with COVID-19 infection experience rapid deterioration from the onset of symptoms into critical illness (2) and with a mortality rate of 61.5% for critical ones within 28 days of hospital admission (3). Treatment of patients with critical illnesses constitutes great pressure on medical services, especially results in the lack of intensive care resources. Therefore, early identification and effective triaging of patients with a high risk of developing critical illness COVID-19 upon admission can aid in improving patient care, increasing the cure rate, and mitigating the burden on the medical care system.

The risk factors for critical illness are not well-revealed. Previous reports have identified that older age, organ dysfunction, neutrophilia, preexisting concurrent cardiovascular or cerebrovascular diseases, coagulopathy, amounts of CD3+CD8+ T cells, and elevated D-dimer levels are associated with the development of acute respiratory distress syndrome and increased mortality risk (1, 4–9). A limited number of publications have identified chest radiographic abnormality, older age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio (10), lactate dehydrogenase (LDH), and direct bilirubin are risk factors associated with the development of critical illness (11, 12). Clinical scores for predicting which patients with COVID-19 will develop critical illness were developed with these above 10 factors (11, 12), which show well-discrimination. In addition, an integrated model was developed with patient history, laboratory markers, and chest radiography at hospital admission to predict critical illness by Schalekamp et al. (13). However, in these models, some diagnoses of co-existing illness and symptoms were from patients' self-reports at admission, which might lead to recall bias.

Mathematical modeling with appropriate inputs can make predictions in the dynamics and control of the infectious disease. A series of mathematical models have been developed on the transmission dynamics and control of COVID-19 or SARS-CoV-2 virus in different countries (14–24), namely, Wuhan, Italy, and the USA. In this retrospective multicenter study, we proposed and extended classical least absolute shrinkage and selection operator (LASSO) logistic regression for the early identification of patients at high risk of progression to critical illness. We systematically analyzed the accessible laboratory findings of confirmed 1,929 patients with COVID-19 having clear prognostic information in 32 hospitals in Hubei and Hunan provinces of China and identified robust and meaningful factors associated with a critical illness. The laboratory findings were measured objectively. A risk prediction model was constructed according to LASSO logistic regression to help identify patients at the time of hospital admission who are at high risk of developing a critical illness. This model aims at distinguishing patients at imminent risk of critical illness, thereby optimizing the allocation of limited healthcare resources and potentially lowering the mortality rate.

METHODS

Data Collection

This study has been proved by the Institute of Clinical Pharmacology, Central South University. For the urgent need to collect and analyze data on this emerging pathogen, the ethics committee of the Institute of Clinical Pharmacology, Central South University granted a waiver of written informed consent from study participants. Medical records of hospitalized patients with COVID-19 diagnosed in 31 hospitals in China (4 hospitals in Hubei Province and 27 hospitals in Hunan Province) were collected. All patients who were diagnosed with COVID-19 by positive high-throughput sequencing or real-time reverse-transcription PCR (RT-PCR) assay for nasal and pharyngeal swab specimens were screened, our study enrolled all adult inpatients ($\geq$18 years old) who were hospitalized for COVID-19 and had an explicit outcome of critical illness. The data were cross-checked by experienced respiratory clinicians. All patients with data on clinical status at hospitalization (laboratory findings, critical illness, and discharge status) were included.

Clinical Outcome

The outcome of this study is a critical illness, which is defined as a composite of invasive ventilation, admission to the intensive care unit (ICU), or fatal of patients with COVID-19 (25). The follow-up time was calculated from the first day of hospitalization to the date of death or discharge, or the censored date (12th April 2020 for the development cohort and 11 June 2020 for the validation cohort).

Potential Predictive Variables

Demographic variables and laboratory findings of patients at hospital admission were collected as potential predictive variables. Demographic variables included age and gender. Laboratory findings were conducted as the first measurement within 2 days after at admission, laboratory indexes with complete measurements for more than 50% of the patients in the development cohort were collected: hematologic (hematokrit, basophils, eosinophils, lymphocytes, monocytes, neutrophils, mean corpuscular volume, hemoglobin concentration, coefficient of variation [CV] and SD of red blood cell volume distribution width [RDW], blood platelet count, thrombocytocrit, red blood cell, and white blood cells), biochemical [levels of glucose, K, Na, total Ca, Cl, total protein, lactate dehydrogenase (LDH), glutamic-pyruvic transaminase, creatine kinase, aspartate transaminase (AST), creatine kinase muscle-brain isoform (CK-MB), creatinine, ureophil, albumin, globulin, albumin to globulin ratio, and glomerular filtration rate (GFR)], coagulation function indexes [levels of D-dimer and fibrinogen, activated partial thromboplastin time (APTT), and prothrombin time (PT)], infection-related indices [levels of C-reactive protein (CRP), procalcitonin (PCT), and alpha hydroxybutyrate dehydrogenase (α-HBDH)], and also the level of uric acid. For the complete laboratory findings and corresponding ratio of missing values, please refer to **Supplementary Table 1**.

Statistical Analysis

Continuous and categorical variables were presented as mean, SD [interquartile range (IQR)], and *n* (%), respectively.

A total of 1,255 patients hospitalized with COVID-19 in the development cohort were included for variable selection. To access the association between the quantitative laboratory findings described above and the occurrence of critical illness, a univariate logistic regression analysis was conducted. Since the odds ratio (OR) is interpreted per unit change, to standardize ORs between variables with a different range, logistic regression analysis was applied to dichotomies data (1 = with the occurrence of critical illness and 0 = without the occurrence of critical illness) with quartiles of each of the 38 laboratory findings modeled as continuous (<25% quartile = 1; ≥25% and <50% quartile = 2; ≥50% quartile and <75% quartile = 3; and ≥ 75% quartile = 4). The associations between the occurrence of critical illness and age (≥55 vs. <55 years) were also evaluated.

The statistically significant 28 covariates ($p < 0.05$) in the univariate logistic analysis were selected as candidates for risk score development of critical illness. A total of 1,064 patients with at least 80% data completeness of the above 28 variables were utilized for model establishment. We applied predictive mean matching to impute numeric features (laboratory findings) with "mice" packages in R for these 1,064 patients.

Prediction models were developed with the LASSO logistic regression, support vector regression (SVR), artificial neural network (ANN), regression tree (RT), and multivariate adaptive regression splines (MARS) machine learning techniques. We used the "glmnet" (14) package for LASSO, "e1071" package for SVR, "RSNNS" package for ANN, "rpart" package for RT, and "earth" package for MARS. Default parameters were used. L1-penalized least absolute shrinkage and selection regression augmented with 1,000-fold cross-validation for internal validation was utilized. LASSO logistic regression is a logistic regression model that penalizes the absolute size of the coefficients of a regression model according to the value of λ. In the process of LASSO regression coefficients, some unimportant regression coefficients can be directly reduced to 0 to achieve the function of variable screening. In comparison to the ridge regression model, the penalty term in the LASSO regression is an absolute value, namely, L1 regular. The estimates of weaker factors shrink toward zero with larger penalties, then only the greatest predictors were left in the model. We select the most predictive covariates by the minimum value of λ. Subsequently, variables identified by LASSO regression analysis were used to construct the risk score with their coefficients:

$$Risk\ Score(RS) = \sum_{i=1}^{n} (Value_i * Coe_i) \quad (1)$$

where n stands for the number of prognostic variables in the model; $Value_i$ is the original value of $variable_i$; and Coe_i is the estimated coefficient of $Value_i$ in the LASSO logistic regression model. The probability of developing critical illness was calculated with the following formula: probability = exp (RS)/[1+ exp(RS)].

We used receiver operating characteristic (ROC) curves to compare the sensitivity and specificity of scores generated with different machine learning techniques. The abscissa and ordinate coordinates of ROC curves are false-positive rate and true probability, respectively. The points of ROC curves reflect the susceptibility to the same signal stimulus. By comparing the false-positive and true numbers, ROC curves show the performance of a classification model at all classification thresholds. The area under the receiver operating characteristics (AUROC), namely, the entire two-dimensional area underneath the entire ROC curve, was used as the precision measurement. AUROC shows how much the model is capable of distinguishing between classes. The larger the AUROC value, the better will be the model at predicting different classes. R-package "ROCR" was utilized for the calculation of the AUROC curve.

To explore temporal changes in laboratory findings during hospitalization, differences between critical illness groups during follow-up in laboratory findings were estimated from linear mixed models with R package "nlme."

Details of samples used at each stage of statistical analysis were depicted in **Figure 1**. All statistical analysis was conducted with R software (version 3.6.2, R Foundation), and *p*-values were computed from two-tailed tests of statistical significance with a type I error rate of 5%.

External Model Validation

To validate the generalizability of the risk scores, we used an independent cohort from hospitals in Hunan province including 566 patients. We collected the same variables required for calculating the risk score from the validation cohort and cross-checked them. The 432 patients with at least 80% data

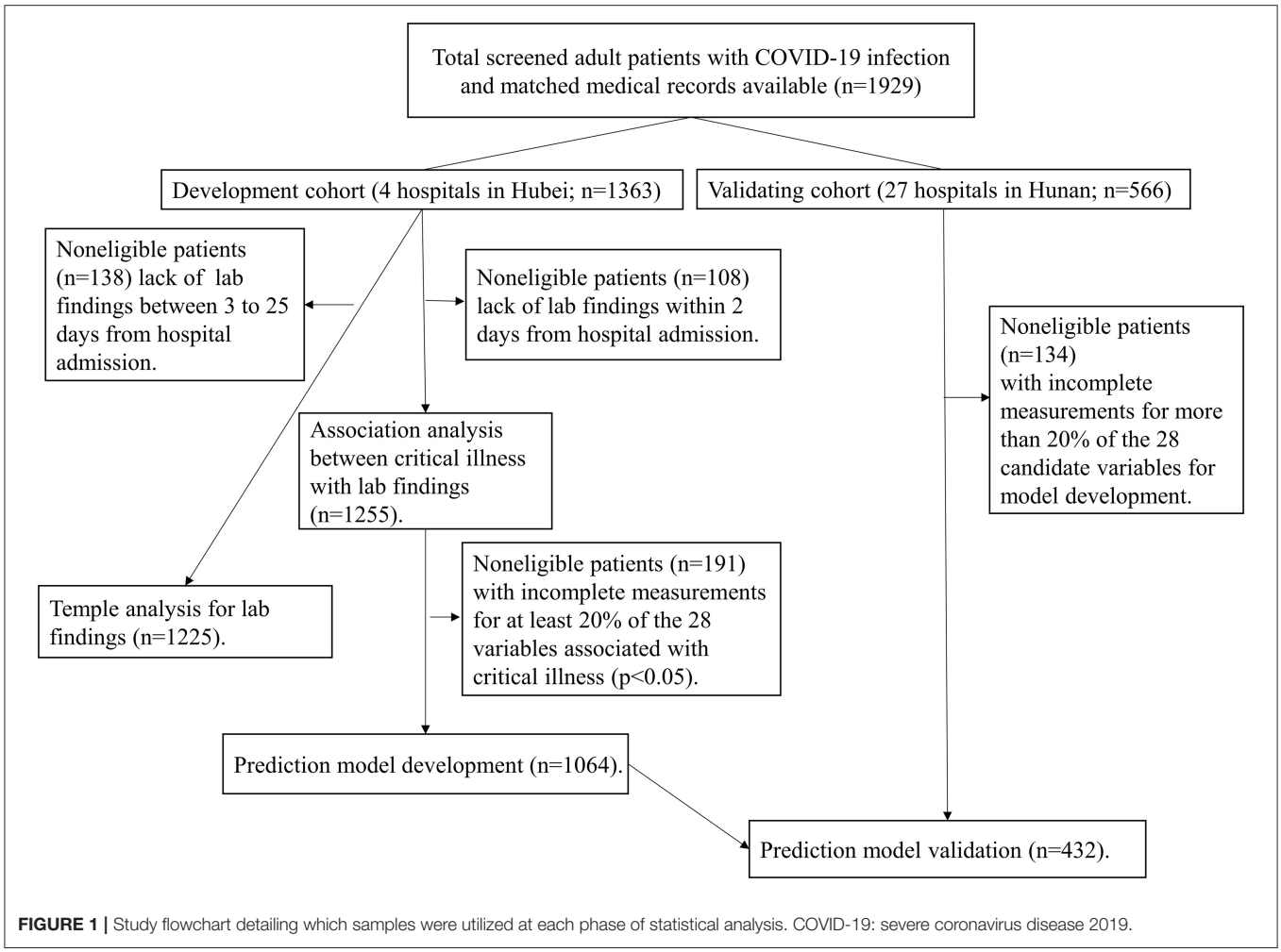

FIGURE 1 | Study flowchart detailing which samples were utilized at each phase of statistical analysis. COVID-19: severe coronavirus disease 2019.

completeness of the 28 variables used for model development were selected. The laboratory findings were imputed and the risk score was calculated as described for the development cohort. To assess the discriminative ability, the AUCs were evaluated.

RESULTS

Characteristics of the Cohorts

The development cohort with 1,363 patients, of which a total of 133 patients eventually developed critical illness (9.8%), from 4 hospitals in Hubei. The median follow-up time for patients was 14 days. The average (SD) age of patients in this cohort was 57.84 (16.29) years; 634 patients (46.52%) were men. The validation cohort included 566 patients with a mean (SD) age of 45.94 (15.33) years, 291 (51.41) were men. The median follow-up time for patients was 13 days. The critical illness eventually developed in 28 (4.24%) of these patients.

Prognostic Factors of Critical Illness

A total of 39 features were tested for associations with critical illness in the development cohort with univariate logistic regression analysis. The results of the 1,255 patients showed that 28 variables were prognosis factors for critical illness COVID-19 ($p < 0.05$, **Table 1**, **Figure 2**). The odds of critical illness were higher in patients older than 65 years. Laboratory results show that elevated CK-MB, neutrophils, PCT, α-HBDH, D-dimer, LDH, glucose, PT, APTT, RDW (SD and CV), fibrinogen, and AST were associated with a critical illness. Patients in the critical illness group showed lymphopenia and had a low rate of basophils, eosinophils, thrombopenia, red blood cell, hematocrit, hemoglobin concentration, and blood platelet count and represented decreased levels of K, Na, albumin, albumin to globulin ratio, and uric acid, compared with the non-critical illness group.

Longitudinal Observations of Laboratory Variables

To determine the major clinical features that appeared during COVID-19 disease progression, the dynamic changes in 28 clinical laboratory parameters were measured within 2 days after hospital admission and associated with critical illness, namely, hematological and biochemical parameters, were recorded from day 3 to day 25 after hospital admission. The temporal changes in laboratory findings during hospitalization were explored

TABLE 1 | Laboratory characteristics among patients who did not or did develop critical illness in the development cohort.

Laboratory tests	Total, mean (SD) [Interquartile range]	Critical illness (n = 1,255)	
		No (n = 1,130)	Yes (n = 125)
Hematologic			
Lymphocytes, $\times 10^9$/L	1.32 (0.67) [0.86–1.66]	1.36 (0.67) [0.9–1.69]	0.94 (0.47) [0.6–1.23]
Eosnophils, $\times 10^9$/L	0.08 (0.14) [0–0.1]	0.08 (0.14) [0.01–0.11]	0.05 (0.13) [0–0.05]
Basophils, $\times 10^9$/L	0.02 (0.02) [0.01–0.03]	0.03 (0.02) [0.01–0.04]	0.02 (0.03) [0.01–0.02]
Neutrophils, $\times 10^9$/L	4.19 (2.85) [2.54–4.76]	4.03 (2.61) [2.5–4.66]	5.57 (4.24) [2.84–7.97]
Blood platelet, $\times 10^9$/L	219.31 (84.12) [161–266]	220.91 (83.06) [164.75–267.25]	205.43 (91.92) [135–263.25]
Thrombocytocrit, %	0.22 (0.08) [0.16–0.27]	0.22 (0.08) [0.17–0.27]	0.19 (0.08) [0.14–0.24]
RDW (CV),%	12.91 (1.45) [12–13.3]	12.86 (1.41) [12–13.3]	13.37 (1.75) [12.22–14.03]
RDW (SD), fL	41.59 (4.48) [38.7–43.7]	41.4 (4.21) [38.7–43.6]	43.27 (6.22) [39.8–45.48]
Hematokrit, %	37.74 (6.04) [34.4–41.5]	37.89 (5.97) [34.7–41.62]	36.32 (6.53) [31.4–40.48]
Hemoglobin concentration, g/L	126.56 (18.71) [116–139]	127.17 (18.37) [117–139]	121.15 (20.8) [107–135]
Red blood cells, $\times 10^{12}$/L	5.12 (11.5) [3.7–4.63]	5.04 (10.56) [3.72–4.66]	5.79 (17.68) [3.35–4.45]
Biochemical			
AST, U/L	29.04 (21.34) [16.7–33.35]	28.51 (21.03) [16.5–32.8]	33.46 (23.4) [18.4–41.5]
CK-MB, U/L	9.51 (9.13) [5–11.4]	9.14 (9.28) [5–10.85]	11.99 (7.56) [7–13.5]
Albumin to globulin ratio, %	1.34 (0.34) [1.11–1.54]	1.35 (0.34) [1.12–1.56]	1.26 (0.34) [1.08–1.44]
Albumin, g/L	37.1 (5.58) [33.4–41.3]	37.27 (5.52) [33.67–41.4]	35.62 (5.92) [31.82–39.5]
LDH, U/L	224.76 (117.43) [153–254]	217.94 (111.64) [151–240]	270.02 (142.8) [173–331.5]
Glucose, mmol/L	6.49 (2.91) [4.93–6.93]	6.37 (2.78) [4.91–6.79]	7.49 (3.66) [5.5–8.09]
K, mmol/L	4.12 (0.54) [3.8–4.44]	4.13 (0.53) [3.8–4.45]	3.98 (0.59) [3.68–4.32]
Na, mmol/L	139.91 (4.29) [137.6–142.7]	140.05 (4.14) [138–142.8]	138.73 (5.34) [135.55–142]
Infection-related indices			
CRP, mg/L	28.8 (41.98) [2.4–40.6]	26.09 (38.96) [2.2–38]	53.9 (57.96) [13.25–64.4]
PCT, ng/ml	0.28 (1.7) [0.04–0.09]	0.17 (0.63) [0.04–0.08]	1.04 (4.38) [0.05–0.22]
α-HBDH, U/L	173.23 (85.83) [120–192]	166.55 (79.52) [117–186]	210.97 (108.1) [145.75–261.75]
Coagulation function			
D-dimer, μg/mL	2.09 (7.43) [0.26–1.45]	1.8 (6.61) [0.24–1.3]	4.29 (11.79) [0.46–3.12]
PT, s	11.57 (1.09) [10.9–12]	11.49 (0.97) [10.8–12]	12.18 (1.61) [11.2–12.6]
APTT, s	28.12 (6.21) [24.4–30.7]	27.78 (6.04) [24.4–30.3]	30.58 (6.89) [25.5–33.9]
Fibrinogen, g/L	3.18 (1.21) [2.31–3.69]	3.15 (1.23) [2.29–3.64]	3.39 (1.06) [2.65–3.98]
Uric acid, umol/L	283.57 (108.58) [212–332]	284.9 (105.29) [214.25–336]	272.18 (133.43) [200–291.5]

RDW, red blood cell volume distribution width; AST, aspartate aminotransferase; CV, coefficient of variation; SD, standard deviation; AST, aspartate aminotransferase; CK-MB, Creatine kinase muscle-brain isoform; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, Procalcitonin; PT, prothrombin time; APTT, activated partial thromboplastin time.

(**Figure 3**). Baseline lymphocyte count was significantly lower in critical illness than in non-critical illness patients. Levels of CRP, D-dimer, LDH, and glucose were clearly elevated in the critical illness group compared with the non-critical illness group throughout the clinical course either in the developing dataset. Furthermore, we found that compared to that in the non-critical illness group, neutrophils, α-HBDH, and globulin were increased in the critical illness group, while eosinophils and albumin were decreased in the critical illness group.

Construction of the Risk Models and their Performances

A total of 28 variables determined at hospital admission and associated with a critical illness (**Figure 2**) were included in the model development. Prediction models were constructed using LASSO logistic regression, SVR, ANN, RT, and MARS, their performance was evaluated by the ROC analysis (**Figure 4**). Although the predictive ability of ANN and SVR in the development cohort was better than other algorithms, the predictive ability using models of LASSO logistic regression and ANN outperformed the other algorithms in the validating dataset (**Figure 4D**). The LASSO logistic regression model was selected by us for its high predictive power and interpretability. In LASSO regression, after excluding irrelevant and redundant features (**Figures 4A,B**), 21 features remained for LASSO regression analysis, including age, whether take ARB drugs and blood test results, lymphocytes, neutrophils, blood platelet, thrombocytocrit, RDW (CV and SD), hematocrit, hemoglobin concentration, AST, CK-MB, albumin, LDH, glucose, K, Na, CRP, PCT, PT, APTT, fibrinogen, and uric acid. The risk score was constructed based on the coefficients from the LASSO logistic model (**Table 2**) and then converted into a probability with

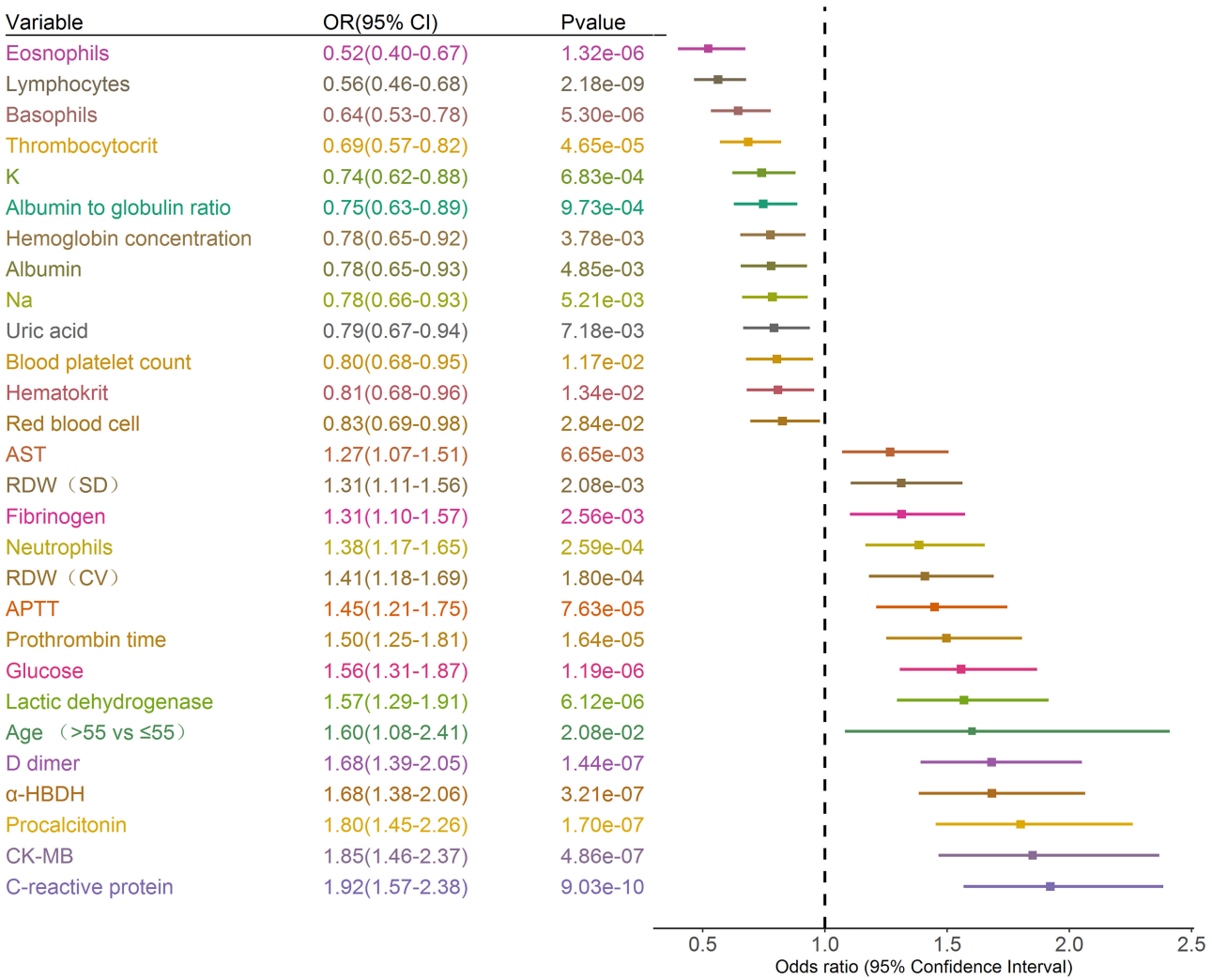

FIGURE 2 | Prognostic associations of clinical characteristics and laboratory findings in the development dataset. Unadjusted ORs (boxes) and corresponding 95% CIs (horizontal lines) for variables associated with the development of critical illness are represented. Box size is inversely proportional to the standard error of OR. The variables are stratified as quartiles. OR, odds ratio. CI, confidence interval.

formulas presented in the method and materials section. By internal 100 times bootstrap validation, the mean AUC based on data from the development cohort was 0.83 (95% CI, 0.78–0.86) (**Figure 4C**). Variables utilized in the risk score for the validation cohort are shown in **Table 3**. The accuracy of the COVID risk score in the validation cohort was like that of the development cohort with an AUC in the validation cohort of 0.84 (**Figure 4D**).

DISCUSSION

Early identification of patients with COVID-19 at risk of progression to critical illness disease will aid in better patient management and effective usage of healthcare resources. In this study, we unraveled that older age and higher levels of laboratory test indexes such as CRP, LDH, and glucose, and lower levels of laboratory findings such as lymphocytes and albumin on admission were associated with higher probabilities of critical illness COVID-19. In addition, a clinical risk score based on LASSO logistic regression was developed to predict the development of critical illness patients with COVID-19 with satisfactory accuracy according to AUC (0.83). Generally, the 21 variables required for estimating the probability of developing critical illness can be easily obtained from routine tests at hospital admission. The robustness and applicability of the risk score were confirmed in the independent validation dataset (AUC = 0.84).

Univariate analyses revealed that factors, namely, age, neutrophils, D-dimer, LDH, CRP, glucose, APTT, fibrinogen, AST, and several other biochemical parameters were associated with a critical illness. In addition, the dynamic profile of the significant laboratory findings was tracked. Levels of LDH, D-dimer, glucose, CRP, α-HBDH, and globulin are higher in the critical illness group compared with the non-critical illness

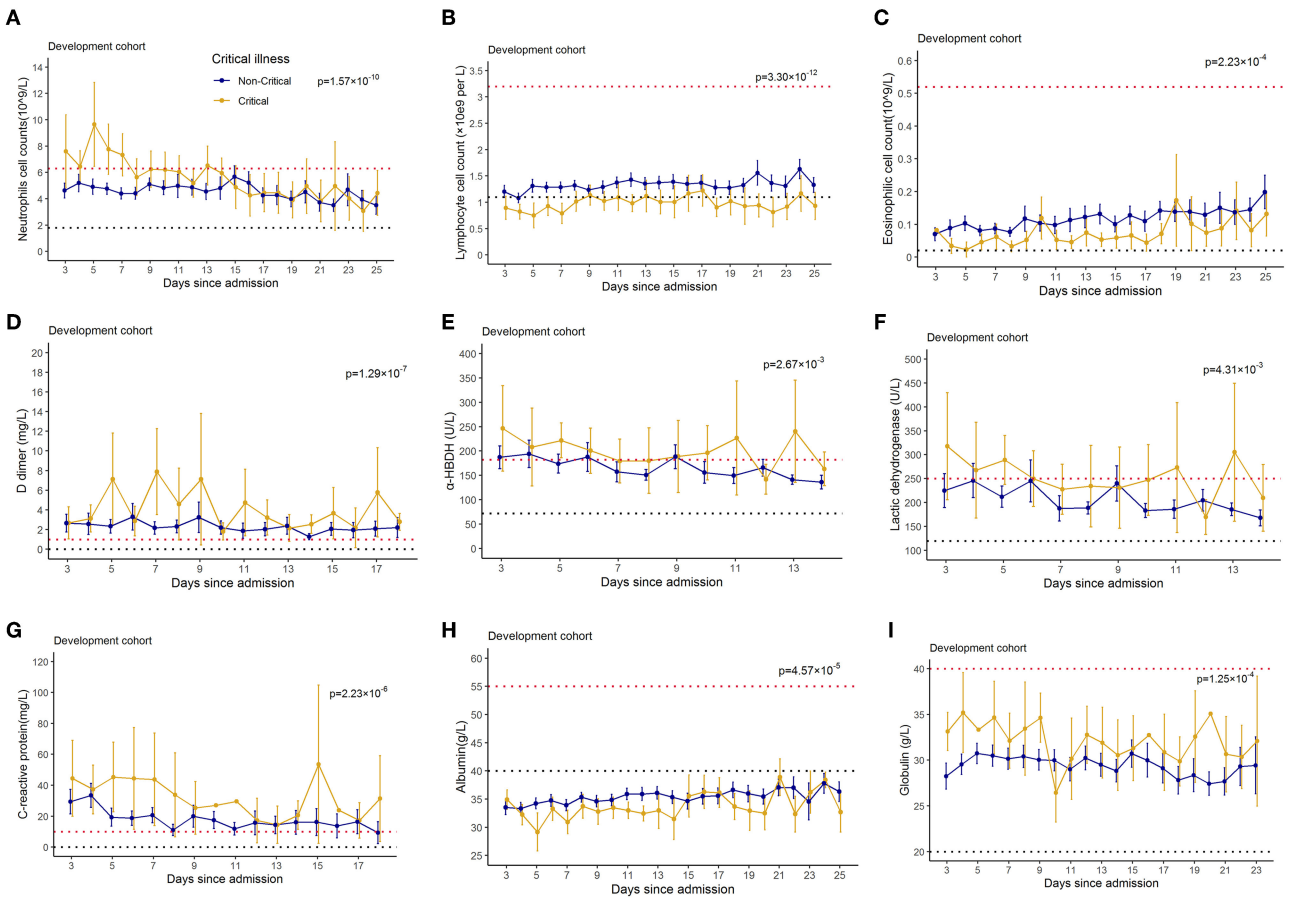

FIGURE 3 | Temporal changes in laboratory findings from illness onset in patients hospitalized with COVID-19. Temporal changes in neutrophils **(A)**, lymphocytes **(B)**, eosinophils **(C)**, D-dimer **(D)**, alpha hydroxybutyrate dehydrogenase **(E)**, lactate dehydrogenase **(F)**, C-reaction protein **(G)**, albumin **(H)**, and glucose **(I)** in the development dataset were presented. Differences between critical illness patients and non-critical illness patients were demonstrated with *p*-values calculated with mixed linear models. The dashed lines in black and red color show the lower and upper normal limits of each laboratory finding.

group. And neutrophil counts and albumin are lower in the critical illness group compared with the non-critical illness group. A prediction model for critical illness was developed with 21 predictors that were found to be independently correlated with critical illness *via* multivariate LASSO logistic regression analysis. Previous studies have found several of these variables to be prognosis factors for patients with COVID-19. It has been reported that elderly patients were more commonly critically ill with COVID-19 (3, 26, 27) and have a higher probability of a death outcome (28, 29). Modelli and colleagues revealed that the 28-day fatality rate was associated with increasing age, hypertension, cardiovascular disease, and higher body mass index (17), in agreement with the previous work.

Lymphopenia, leukocytosis (with increased absolute neutrophil counts), eosinopenia, neutrophilia, increased CRP and PCT which reflects a persistent state of inflammation (30) may be related to cytokine storm and cellar immune deficiency induced by virus invasion (27, 31). Zhou et al. found lower lymphocyte counts and higher LDH in patients who died from COVID-19 (1). Injured alveolar epithelial cells could lead to the infiltration of lymphocytes, resulting in persistent lymphopenia (32, 33). Lymphopenia is a common characteristic in patients with COVID-19 and might play an important role in the disease process (34, 35). Zhang et al. noted that 53% of patients admitted with COVID-19 had eosinopenia on the day of hospital admission (36). Calabrese et al. reported that lymphocyte and platelet counts were the most important features able to stratify patients into different clinical clusters (37). Ewan et al. demonstrated that risk stratification was improved by blood and physiological parameters (C-reactive protein, neutrophil/lymphocyte ratio, and neutrophil count) measured at hospital admission (20). Such findings were consistent with this work. A higher level of LDH was an indication of the activity and severity of idiopathic pulmonary fibrosis and is one of the most important prognostic biomarkers of lung injury (37). LDH was reported to be higher in severe and patients who received ICU treatment with COVID-19 than in mild and non-ICU patients (27, 30, 38, 39), which is utilized as a valuable prognosis

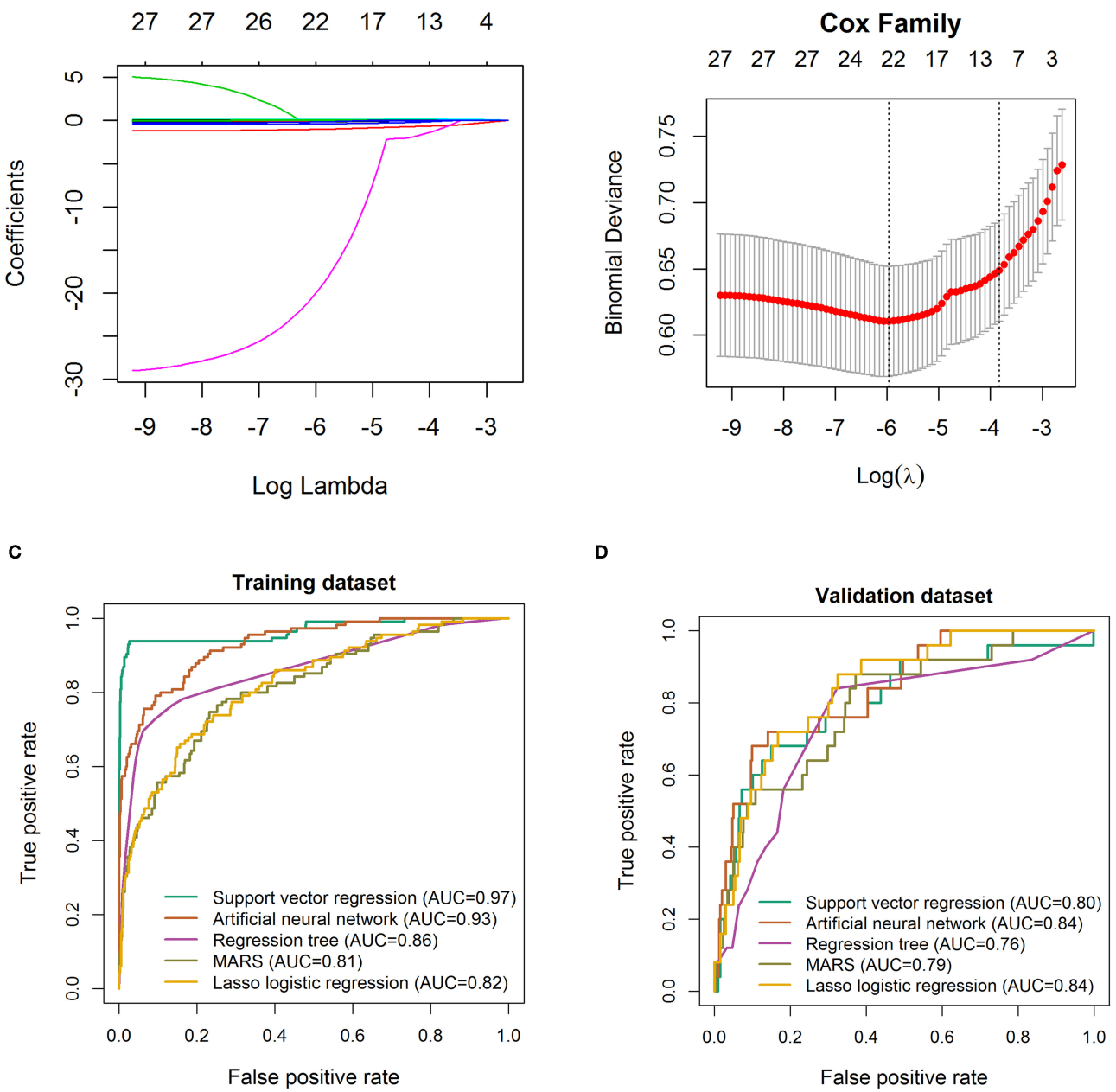

FIGURE 4 | Feature selection using the least absolute shrinkage and selection operator (LASSO) logistic regression model. **(A)** LASSO coefficient profiles of the 29 baseline features. **(B)** Tuning parameter (λ) selection in the LASSO model used 1,000-fold cross-validation *via* minimum criteria. Receiver operating characteristic curve for the performance of different machine learning techniques to distinguish individuals with COVID-19 from those with critical illness COVID-19 in the training cohort **(C)** and validation cohort 1 **(D)**, respectively. AUC, area under the receiver operating characteristic curve. The true positive rate represents module sensitivity, whereas the false positive rate is one minus the specificity.

predictor (40, 41). In addition, patients with elevated CK-MB levels on hospital admission were at significantly increased risk of critical illness. Li and colleagues found that cardiac injury (elevated LDH and CK-MB levels) were associated with severe disease or ICU admission and death in patients with COVID-19 (42). Increased PT and APTT, decreased blood platelet, thrombocytocrit, and fibrinogen which reflect the coagulation activation might be associated with the sustained inflammatory

TABLE 2 | Coefficients of LASSO logistic regression model for predicting development of critical illness in 1,064 patients hospitalized with COVID-19 in the development dataset.

Laboratory tests	Coefficient
Lymphocytes, $\times 10^9$/L	−1.0049
Neutrophils, $\times 10^9$/L	0.085
Blood platelet, $\times 10^9$/L	0.017
Thrombocytocrit, %	−19.7385
RDW(CV),%	0.0601
RDW(SD), fL	0.0395
Hematokrit, %	−0.003
Hemoglobin concentration, g/L	−0.0015
Glucose, mmol/L	0.1131
K, mmol/L	−0.3833
Na, mmol/L	−0.0187
AST, U/L	−0.0026
CK-MB, U/L	0.0037
Albumin, g/L	0.0096
PT, s	0.1381
APTT, s	0.0148
Fibrinogen, g/L	−0.1319
CRP, mg/L	0.0033
PCT, ng/ml	0.1068
α-HBDH, U/L	0.0005
Uric acid, umol/L	−0.0025

RDW, red blood cell volume distribution width; AST, aspartate aminotransferase; CV, coefficient of variation; SD, standard deviation; AST, aspartate aminotransferase; CK-MB, Creatine kinase muscle-brain isoform; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, Procalcitonin; PT, prothrombin time; APTT, activated partial thromboplastin time.

response. Banoei et al. noted that prothrombin and lactate were the most differentiating biochemical markers in the mortality prediction model (18).

Since hyperglycemia is harmful to the management of inflammation and viremia, the association between the level of glucose and critical illness in COVID-19 viral infections is not surprising. Based on big data analysis with a cohort with 7,337 COVID-19 cases, Zhu et al. revealed that diabetics with better-controlled blood glucose were associated with a decreased death risk than diabetics with poorly controlled blood glucose (43). Banoei and colleagues demonstrated that disease, coronary artery disease, dementia, age > 65, and altered mental status were the topmost differentiating mortality predictors (22).

Previous studies have identified that 15–53% of cases reported abnormal levels of AST during disease progression (44–47). In a study conducted by Huang et al. (48), the elevation of AST was found in 8 (62%) of 13 patients in the ICU compared with 7 (25%) of 28 COVID-19 infected cases who did not need ICU care. Abnormal liver tests occur in most hospitalized patients with COVID-19 and may be associated with ICU admission, mechanical ventilation (48), and death (28, 48). Liver damage (decreased albumin and increased globulin) in patients with COVID-19 infections might be associated with the direct effect of the viral infection of liver cells, drug hepatotoxicity, or immune-mediated inflammation (37), such as cytokine storm and pneumonia-associated hypoxia.

Prediction models for the dynamic and control of COVID-19 infection found broad similarities with the features retained in our models, particularly regarding aging, hypertension, CRP, LDH, prothrombin, lactate, and neutrophil levels (14–24). The main advantage of the LASSO logistic regression is that the variable with a large parameter estimation is compressed to a smaller variable, while the variable with the smaller parameter estimate is compressed to 0. The parameter estimation of the LASSO analysis is continuous, which is suitable for model selection with high-dimensional data.

In the development dataset, we found that the discriminative abilities of SVR, ANN, RT, and MARS were outperforming that of LASSO logistic regression as evaluated by AUCs. However, in the independent validation dataset, the predictive ability of LASSO logistic regression was the best within all algorithms and was selected by us. The phenomenon that the model that incorporates the highest level of non-linearity displayed better in-sample prediction, but also yielded the worse out-of-sample performances may account for the over-fitting problem of the ANN, RT, MARS, and SVR algorithms (45). The linear Kernel function utilized in LASSO logistic regression performed badly in-sample but generated the best out-of-sample predictions.

There are inevitably limitations in our retrospective study. The primary one is incomplete laboratory findings in the electronic database and the lacking of CT images, which decreases the statistical power of the LASSO logistic regression model. Therefore, important information might be missed and further prospective studies are required. However, our model has a certain tolerance to missing data, as high performance as measured by AUC on the developing and external validation dataset for samples missing 20% of the predictors was achieved. Second, since the algorithms we tried are purely data-driven, the performances of these models may vary if developed with different datasets. We believe that more accurate models can be obtained with the increasing of available datasets. Third, the data for risk probability development and validation are from two provinces of China, which could potentially limit the generalizability of the risk model. Further studies on different populations all over the world with larger patient cohorts are needed to validate our findings.

CONCLUSION

In summary, this study identified 28 indicators (such as age, LDH, CRP, and lymphocytes) associated with critical illness of patients with COVID-19. The longitudinal laboratory variables were explored. A risk score to estimate the risk of developing critical illness among patients with COVID-19 was developed based on 21 variables independently associated with critical

TABLE 3 | Laboratory characteristics of patients with COVID-19 in validation cohort.

Laboratory tests	Total, mean (SD) [Interquartile range]	Critical illness ($n = 566$)	
		No ($n = 538$)	Yes ($n = 28$)
Hematologic			
Lymphocytes, $\times 10^9$/L	1.23 (0.57) [0.82–1.55]	1.26 (0.57) [0.86–1.58]	0.78 (0.35) [0.53–1.03]
Neutrophils, $\times 10^9$/L	3.71 (2.66) [2.19–4.23]	3.61 (2.60) [2.15–4.16]	5.52 (3.11) [2.97–8.07]
Blood platelet, $\times 10^9$/L	192.7 (74.34) [139–233]	194.46 (74.95) [139–234.25]	144.38 (25.92) [131–154]
Thrombocytocrit, %	0.2 (0.07) [0.15–0.24]	0.2 (0.07) [0.15–0.24]	0.17 (0.05) [0.14–0.2]
RDW(CV),%	12.39 (1.24) [11.8–12.7]	12.37 (1.21) [11.8–12.7]	12.88 (1.63) [11.9–13.45]
RDW(SD), fL	39.65 (3.28) [37.5–41.4]	39.61 (3.25) [37.5–41.4]	40.67 (3.81) [38.1–43.08]
Hematokrit, %	37.39 (10.86) [35.3–42.9]	37.52 (10.9) [35.38–43]	35.05 (10.05) [33.58–39.08]
Hemoglobin concentration, g/L	132.59 (21.4) [122–147]	133.1 (20.97) [122–147]	123.96 (26.73) [119–141]
Biochemical			
Glucose, mmol/L	7.19 (3.41) [5.34–7.87]	7.08 (3.26) [5.31–7.7]	9.03 (5.23) [6.26–9.19]
K, mmol/L	3.97 (0.47) [3.64–4.24]	3.98 (0.46) [3.67–4.24]	3.79 (0.65) [3.44–4.13]
Na, mmol/L	138.9 (3.42) [137–140.91]	139.01 (3.42) [137.2–141]	136.61 (2.63) [136–137.8]
AST, U/L	29.75 (15.4) [20–34]	29.06 (14.75) [20–33]	43.06 (21.16) [24.1–54.6]
CK-MB, U/L	13.83 (6.78) [9.99–16.73]	13.67 (6.74) [9.8–16.12]	16.83 (6.87) [13–20.11]
Albumin, g/L	40.81 (5.03) [37.92–44.1]	41.05 (4.93) [38.3–44.4]	36.16 (4.75) [33.5–40.2]
Infection-related indices			
CRP, mg/L	22.55 (30.41) [2.9–28.3]	20.48 (28.26) [2.67–26.1]	59.27 (42.61) [25.27–95.5]
PCT, ng/ml	0.08 (0.13) [0.04–0.08]	0.07 (0.09) [0.04–0.08]	0.21 (0.37) [0.04–0.18]
α-HBDH, U/L	200.1 (81.44) [149.68–229.1]	193.16 (76.59) [144.5–221.75]	273.63 (98.73) [203.57–307.15]
Coagulation function			
PT, s	11.81 (2.29) [10.7–12.7]	11.69 (1.38) [10.7–12.7]	13.95 (7.69) [11.62–13.2]
APTT, s	31.63 (7.9) [27.55–35.8]	31.28 (7.33) [27.2–35.5]	37.42 (13.41) [31.12–41.9]
Fibrinogen, g/L	6.74 (34.13) [2.93–4.54]	6.89 (35.15) [2.92–4.5]	4.22 (1.24) [3.5–4.99]
Uric acid, umol/L	265.51 (89.47) [202.05–319.18]	267.98 (88.84) [206.1–320.52]	217.79 (89.99) [154.9–254]

RDW, red blood cell volume distribution width; AST, aspartate aminotransferase; CV, coefficient of variation; SD, standard deviation; AST, aspartate aminotransferase; CK-MB, Creatine kinase muscle-brain isoform; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, Procalcitonin; PT, prothrombin time; APTT, activated partial thromboplastin time.

illness and commonly measured on hospital admission. The risk model is especially valuable for early detection and intervention of the incidence of critical illness COVID-19, thus making improvements to clinical strategies against COVID-19, optimizing the use of healthcare resources, and potentially reducing mortality in patients with COVID-19.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

YF: conceptualization and writing. WZho: resources and data curation. TL, JL, KX, XM, LX, and JJ: resources. HZ: supervision. RL: project administration and supervision. WZha: funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Clinical Analysis of Acute Organophosphorus Pesticide Poisoning and Successful Cardiopulmonary Resuscitation: A Case Series

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Acute organophosphorus pesticide poisoning (AOPP) with cardiac arrest has an extremely high mortality rate, and corresponding therapeutic strategies have rarely been reported. Therefore, this study aimed to explore the prognostic factors and effective treatments of AOPP-related cardiac arrest. This retrospective study was conducted in our department in the years 2018–2021. We conducted a descriptive analysis of the clinical manifestations, rescue strategies, and prognosis of patients with AOPP who had experienced cardiac arrest and successful cardiopulmonary resuscitation. This study included six cases of patients with AOPP in addition to cardiac arrest; in four cases, cardiac arrest occurred < 12 h after ingestion, and in two, cardiac arrest occurred more than 48 h after ingestion. Five patients had not undergone hemoperfusion therapy before cardiac arrest, and all six were treated with atropine during cardiopulmonary resuscitation and subsequent pralidoxine. Four patients recovered and were discharged from the hospital, one died in our department, and one was transferred to a local hospital and died there 2 h later. The last two patients had severe pancreatic injuries and disseminated intravascular coagulation. This, along with their death, might have been related to their prognosis. Cardiac arrest can occur in patients with severe AOPP for whom antidote administration was insufficient or not timely. Application of atropine and pralidoxine in a timely manner after cardiac arrest following AOPP is the key to successful treatment. This study provides useful guidelines for the treatment of similar cases in the future.

Keywords: organophosphorus pesticide, poisoning, cardiac arrest, cardiopulmonary resuscitation, atropine

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INTRODUCTION

Some organophosphorus pesticides (OPs) are extremely poisonous and cause rapid intoxication-induced death with minimal ingestion or exposure. Acute organophosphorus pesticide poisoning (AOPP) is a major life-threatening toxic disease in the rural areas of developing countries (1, 2). In China, AOPP cases comprise nearly 50% of all poisoning cases, with case fatality rates of 3–40%, comprising over 80% of all poisoning deaths (3, 4). OPs cause damage to multiple organs through cholinergic and non-cholinergic effects (5). Common symptoms of AOPP include central nervous system and neuromuscular complications, with cardiopulmonary arrest being the most serious complication and often having a very poor prognosis (6, 7). However, AOPP-related cardiac arrest is rarely reported. In this study, we analyzed the clinical data of patients with AOPP who experienced cardiopulmonary arrest and successful cardiopulmonary resuscitation (CPR) on-site and summarized the clinical characteristics and prognostic factors of the aforementioned disease.

MATERIALS AND METHODS

Study Participants

Six patients with AOPP who suffered a cardiac and/or respiratory arrest and were successfully resuscitated on-site were selected as research participants. These patients had been admitted to the Department of Poisoning and Occupational Diseases, QILU Hospital of Shandong University (Jinan City, China) between January 1, 2018 and December 31, 2021.

Inclusion and Exclusion Criteria

The inclusion criteria included a patient age of ≥18 years, patients who ingested OPs orally, a time from ingestion to admission to our department of <48 h, and meeting the following diagnostic and exclusion criteria. The diagnostic criteria were a clear history of taking poison, a distinct garlic or petroleum odor after ingestion, a reduced acetylcholinesterase level, a cholinergic crisis, and a positive trial of atropine. Patients with previous heart disease or other diseases, such gastroenteritis, myasthenia gravis, Guillain-Barré syndrome, botulism, mushroom toxicity, and nicotine toxicity, were excluded.

Treatment Plan

When patients were transferred to our department, blood and urine routine examinations, along with coagulation function, liver function, renal function, creatine kinase-MB, amylase, lipase, blood glucose, blood lipids, electrolyte, and cholinesterase tests, were conducted. Moreover, other related examinations were obtained. The main conventional treatment drugs included penehyclidine hydrochloride injection (1 mg, twice daily), atropine (1 mg, every 6 h and adjusted as necessary), pralidoxime iodide (2.0 g, twice daily), betamethasone (8 mg, once daily), pantoprazole (40 mg, twice daily), reduced glutathione (1.8 g, once daily), alanyl glutamine (20 g, once daily), torsemide (20 g, twice daily), nalmefene (0.1 mg, twice daily), and fat emulsion, amino acid (8), and glucose (1%) injections (1,920 mL, once daily). Hemoperfusion was administered twice in the first 24 h of admission and subsequently once daily for a total of four times, which was a treatment plan that we called the "2-1-1 plan." The treatment plan was adjusted appropriately based on disease progression. When a cholinergic crisis occurred, atropine was given in a timely manner, and when cardiac and/or respiratory arrest occurred, CPR was immediately performed, and atropine was administered simultaneously. All patients after CPR were timely treated with pralidoxime. We also administered smectite powder and injected activated carbon with mannitol into the patients' stomach through a gastric tube for gastrointestinal decontamination.

Data Collection and Analysis

The patient data described in this paper were obtained from the Department of Poisoning and Occupational Diseases, QILU Hospital of Shandong University (Jinan City, China). We conducted a descriptive analysis of the whole medical record related to this study. Data on the sex, age, type of poison, medical history, main treatment, and condition changes (e.g., prehospital treatment, treatment with CPR, and disease progression) of each patient were obtained. Continuous variables are presented as means ± standard deviations, and categorical variables are presented as counts or actual numerical values.

Registration and Ethics

This study was approved by the Ethics Committee of the Shandong University QILU Hospital (Jinan City), and written informed consent was obtained from the families of patients.

RESULTS

Six patients with AOPP were included in the study. There was one man and five women who were aged 49–66 years, with an average age of 56.8 ± 6.0 years. This research involved four cases of dichlorvos poisoning, one of chlorpyrifos poisoning, and one of dimethoate poisoning. All six patients developed cardiac arrest and were administered atropine by intravenous injection during CPR. Five patients received endotracheal intubation and mechanical ventilation during CPR, and one received mechanical ventilation before cardiac arrest because of respiratory failure. Five patients had not undergone hemoperfusion before the onset of cardiac and/or respiratory arrest. After treatment, four patients recovered and were discharged, and two died. The main clinical data of patients are shown in **Table 1**.

Four patients who had lower cholinesterase levels on admission had cardiac arrest < 12 h after ingestion, that is, when they were immediately transferred to a local hospital or our hospital. Two patients who were administered reduced atropine and/or pralidoxime iodide had cardiac arrests on the fifth day and third day after ingestion, respectively. Both of the patients who died had severe pancreatic injury (amylase and/or lipase levels were three times higher than baseline values) and abnormal coagulation on admission. The patients' main laboratory tests results are shown in **Table 2**.

TABLE 1 | Clinical data of six patients with acute organophosphorus pesticide poisoning.

Patient	Sex (F/M)	Age (y)	Pesticide	Prehospital gastric lavage (Y/N)	Hemoperfusion before cardiac arrest (Y/N)	Endotracheal intubation and mechanical ventilation	Dosage of atropine during CPR	Time to enter our department after ingestion	Time of cardiac arrest	Prognosis
Patient 1	F	66	Chlorpyrifos	Y	N	During CPR	2 mg (one time)	1.5 h	Occurred 2.5 h after ingestion	Recovered
Patient 2	F	56	Dichlorvos	Y	N	During CPR	5 mg (1 mg, 2 mg, 2 mg)	14 h	When transferred to the local hospital	Death
Patient 3	F	50	Dichlorvos	Y	N	10 h before cardiac arrest	3 mg (2 mg, 1 mg)	12 h	Occurred 15 min after being transferred to our department	Recovered
Patient 4	F	62	Dichlorvos	N	N	During CPR	10 mg (5 mg, 5 mg)	10 h	When transferred to the local emergency department	Death
Patient 5	M	49	Dimethoate	Y	N	During CPR	2 mg (1 mg, 1 mg)	2 d	Occurred 5 d after ingestion	Recovered
Patient 6	F	58	Dichlorvos	Y	Y	During CPR	5 mg (2 mg, 2 mg, 1 mg)	2 h	Occurred 58 h after ingestion	Recovered

F, female; M, male; Y, yes; N, no; and CPR, cardiopulmonary resuscitation.

TABLE 2 | Main laboratory test results of six patients upon admission to our department.

Inspection item	Normal range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
CHE (IU/L)	4,650–10,440 IU/L	<200	<200	<200	<200	497.	201
pH	7.35–7.45	7.36	7.21	7.27	7.02	7.35	7.26
Lac (mmol/L)	0.5–2.2 mmol/L	2.9	1.2	1.4	1.1	6.7	1.0
CK (IU/L)	30–135 IU/L	NA	224	88	NA	158	NA
ALT (IU/L)	9–52 IU/L	15	120	27	91	18	17
AST (IU/L)	14–36 IU/L	25	159	32	136	24	34
CK-MB (ng/ml)	0.3–4.0 ng/mL	1.6	18.7	6.5	48.2	6.0	9.2
Amylase (IU/L)	30–110 IU/L	NA	1,611	254	2,509	67	349
Lipase (IU/L)	23–300 IU/L	NA	3,134	99.76	326	37	218
PT (s)	11–14.5 s	14.4	17.4	25.8	25.5	10.4	13.3
PT-INR	0.8–1.2	1.11	1.46	1.23	2.32	0.9	1.01
APTT (s)	28–45 s	28.4	37.5	>180	73.3	24.8	39.1
D-dimer (μg/mL)	0–0.5 μg/mL	5.09	11.33	2.3	>20	0.35	0.65
Fib (g/L)	2–4 g/L	2.72	1.76	3.99	0.60	3.13	3.93
FDP (μg/L)	0–5 μg/L	19.29	42.05	7.52	>150	NA	2.22

CHE, cholinesterase; pH, pondus hydrogenii; Lac, lactic acid; CK, creatine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB; PT, prothrombin time; PT-INR, prothrombin time normalized ratio; APTT, activated partial thromboplastin time; Fib, plasma fibrinogen; FDP, fibrinogen degradation product; NA, not available.

DISCUSSION

In this study, we analyzed the clinical data of patients with AOPP who experienced cardiopulmonary arrest and successful CPR on-site. We found that cardiac arrest occurred in patients with severe AOPP for whom antidote application was insufficient or untimely. Therefore, we assumed that cardiac arrest was related to the toxic effect of OPs and administration of an insufficient amount of a specific antidote.

AOPP is a toxic disease having a main symptom of a cholinergic crisis, leading to the phosphorylation of serine residues in the active site of acetylcholine esterase (AChE) and

gradual inhibition of AChE (9). The reactivation of AChE *in vivo* is key to the successful treatment of AOPP. The main treatment includes atropine, oxime drugs, the removal of toxins *in vivo*, and symptomatic supportive treatment (10–12). The determination of AChE activity can be used as an important index for the diagnosis, grading, and judgment of AOPP. OPs can inhibit acetylcholinesterase and butyrylcholinesterase, although the inhibition of butyrylcholinesterase does not produce clinical symptoms for the most part (13). In China, nearly all clinical hospitals only detect serum levels of cholinesterase, that is, butyrylcholinesterase; therefore, determining a response to AOPP therapy based on butyrylcholinesterase is not completely reliable (14, 15). The lack of a specific antidote or an impertinent rapid diagnosis and disease evaluation leads to improper treatment (16). Atropine and oxime-type antidotes should be applied in a timely manner for AOPP. If the cholinergic crisis induced by AOPP cannot be treated in a timely manner, it is highly likely to progress to cardiopulmonary arrest (17).

In patients with severe AOPP, OPs may cause central apnea or hypopnea (8), and a cholinergic crisis can lead to increased airway secretion, acute cholinergic respiratory failure, and respiratory arrest (18). OPs can also inhibit heart function and cause bradycardia and cardiac arrest. Hypoxemia, electrolyte derangements, and acidosis are major predisposing factors for cardiac arrest (19), and close monitoring and airway management are essential for prevention. The initial dose of atropine for adults is 2 to 5 mg intravenously, and if the patient does not respond to treatment, the dose must be doubled every 3 to 5 min until respiratory secretions have cleared and there is no bronchoconstriction. In severe cases, treatment may require continuous infusion over several days; at first, the toxicants in the gastrointestinal tract are not completely removed, although atropine temporarily alleviates symptoms of cholinergic crisis. However, the amount of antidote in the body remains relatively insufficient, and a cholinergic crisis can easily occur. Thus, once a patient experiences cardiac and/or respiratory arrest, atropine and oxime-type antidotes should be administered simultaneously with CPR (18, 19). In this study, patients who had successful CPR had the common characteristic of the application of atropine and establishment of advanced airway management during on-site resuscitation.

Atropine only works on muscarinic receptors, and pralidoxime works by reactivating the phosphorylated AChE by binding to OPs. The detoxification of oxime, as a specific antidote for AOPP, has saved many lives through early appropriate intervention (20–22). The standard of care includes a bolus of at least 30 mg/kg over 30 min. After the bolus, a continuous infusion of at least 8 mg/kg/h should be initiated and may be needed for several days. However, for the detoxification of oxime to work, it need to be given within 48 h of poisoning. Animal studies have shown that pralidoxime can contribute to the successful resuscitation of cardiac arrest in organophosphate-induced pig models (23). The outlook for most patients is excellent, although cardiac arrest occurred in some severe cases (3). However, owing to the limitation in the acetylcholinesterase structure-based design of oxime antidotes for AOPP, some detoxification effects are limited for some OPs (24, 25). Gastrointestinal decontamination and hemoperfusion (26) can remove OPs in the gastrointestinal tract and blood, respectively. Therefore, the timely and complete removal of toxins is another essential treatment for AOPP. This can also reduce the incidence of poisoning rebound and reduce the incidence of cardiopulmonary arrest.

The suitable dose of atropine for AOPP-related cardiac arrest has not been reported yet. In a previous edition of the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (2020), atropine was not involved in CPR (27), and in a consensus of clinical experts on the diagnosis and treatment of AOPP (2016) in China (4), it had suggested that atropine should be actively administered for AOPP-related cardiac arrest; however, the exact dose was not discussed. In this paper, we observed that the practical dose of atropine during CPR was between 2 and 10 mg for patients undergoing an AOPP-induced cardiac arrest. Due to the limitation of only six patients in this study, the optimal dose of antidotes is not entirely clear, and further research is warranted.

Patients with severe AOPP must be timely evaluated after receiving treatment, and antidotes, such as atropine and pralidoxime, should be administered as soon as possible. Hemoperfusion, gastrointestinal decontamination, and respiratory support treatment should be administered when necessary. For patients with respiratory and cardiac arrest, atropine and pralidoxime are of great importance during CPR. We believe that our findings could potentially provide guidelines for the treatment of AOPP-related cardiopulmonary arrest. Further studies should be conducted to determine the dose and administration time of specific antidotes during CPR.

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/s.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Shandong University Qilu Hospital (Jinan City). Written informed consent was obtained from the patients' families. 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

GY conceived the study, drafted the manuscript, and all authors contributed substantially to its revision. GY, YL, TJ, and LZ supervised the conduct of the paper and data collection. GY, XJ,

YL, LS, SC, and LZ provided statistical advice on the study design and analyzed the data. BK and XJ chaired the data oversight committee. GY and YL take responsibility for the paper as a whole. All authors contributed to the article and approved the submitted version.

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Telephone Triage for Emergency Patients Reduces Unnecessary Ambulance Use: A Propensity Score Analysis With Population-Based Data in Osaka City, Japan

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Background: Telephone triage service in emergency care has been introduced around the world, but the impact of this service on the emergency medical service (EMS) system has not been fully revealed. The aim of this study was to evaluate the effect of telephone triage service for emergency patients on decreasing unnecessary ambulance use by analysis with propensity score (PS) matching.

Methods: This study was a retrospective observational study, and the study period was the 4 years from January 2016 to December 2019. We included cases for which ambulances were dispatched from the Osaka Municipal Fire Department (OMFD). The primary outcome of this study was unnecessary ambulance use. We calculated a PS by fitting a logistic regression model to adjust for 10 variables that existed before use of the telephone triage service. To ensure the robustness of this analysis, we used not only PS matching but also a multivariable logistic regression model and regression model with PS as a covariate.

Results: This study included 868,548 cases, of which 8,828 (1.0%) used telephone triage services and 859,720 (99.0%) did not use this service. Use of the telephone triage service was inversely associated with the occurrence of unnecessary ambulance use in multivariate logistic regression model (adjusted OR 0.453, 95% CI 0.405–0.506) and multivariate logistic regression model with PS as a covariate (adjusted OR 0.514, 95% CI 0.460–0.574). In the PS matching model, we also revealed same results (crude OR 0.487, 95% CI 0.425–0.588).

Conclusions: In this study, we were able to statistically evaluate the effectiveness of telephone triage service already in use by the public using the statistical method with PS. As a result, it was revealed that the use of a telephone triage service was associated with a lower proportion of unnecessary ambulance use in a metropolitan area of Japan.

Keywords: telephone triage, ambulance, EMS, public health, propensity score

INTRODUCTION

The emergency medical service (EMS) is essential social system around the world. However, unnecessary ambulance use and frequent ambulance request are problems of public health in many countries (1–3). In Japan, anyone can call for an ambulance free for charge, and the number of ambulance dispatches has been increasing in recent years (4). As a result, the time duration from ambulance call to hospital arrival is being prolonged (4), and problems such as difficulty in hospital acceptance are occurred by increasing number of patients transported by ambulance (5). This may affect ambulance dispatch to truly emergency patients such as cardiopulmonary arrest and severe trauma with shock.

A telephone triage service in emergency care has been introduced in many countries such as the United Kingdom, Canada and Australia. In these countries, telephone triage nurses use a software to assess the urgency of a patient and provide necessary services such as ambulance dispatch and sending a doctor (6–8). In Japan, a telephone triage service in emergency care was introduced in Tokyo in 2007 and Osaka in 2009. As we previously described the telephone triage service in Osaka, a telephone triage nurse assesses the urgency of the caller with software and dispatches an ambulance or directs the caller to an available medical facility based on the triage result (9). Eastwood et al. revealed that planned emergency department (ED) visits were more likely to be ED suitable than unplanned ED visits (OR 1.62; 95%CI: 1.5–1.7) (8). Another study revealed that all secondary telephone triage cases referred for emergency ambulance dispatch had transportation rates higher than all metropolitan emergency ambulance cases (82.2% vs. 71.1%) (10). However, the effect of the telephone triage service on the EMS system has not been fully revealed. If it reveals that a telephone triage service has positive effect on the EMS system, it is likely that such a service will be introduced in more countries.

Osaka city is one of the largest urban areas in Japan. A telephone triage service was introduced in 2012, and the annual number of ambulance dispatches is approximately 250,000 (11). In this study, we assessed the effect of telephone triage service for emergency patients on the decrease in unnecessary ambulance use by analysis with propensity score (PS).

METHODS

Study Design, Setting, and Populations

This was a retrospective observational study, and the study period was 4 years from January 2016 to December 2019. Osaka city is one of the largest metropolitan areas in Japan, covering an area of 225.30 km^2 with a population of 2.75 million (12). In Japan, the telephone triage service in emergency care and call for ambulance are public services, and anyone can use these services free of charge. In this study, the inclusion criteria were cases for which ambulances were dispatched from the Osaka Municipal Fire Department (OMFD), and the exclusion criteria were cases in which more than one patient was transported by ambulance or cases with missing data. Because we used anonymized data provided from the OMFD, the requirement of obtaining patients' informed consent was waived. This study was approved by the Ethics Committee of Osaka University Graduate School of Medicine (approval number: 16070). We wrote this manuscript based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the reporting of cohort and cross-sectional studies (13).

Telephone Triage Service in Osaka Prefecture

The telephone triage service in Osaka prefecture has been previously described in detail (9). A telephone triage nurse evaluates the urgency of a patient's signs and symptoms using software based on the telephone triage protocol in Japan. This protocol is categorized according to 98 chief complaints (14), and the urgency of the caller is judged by selecting signs and symptoms related to the caller's chief complaints. Similar to telephone triage services in the United States, Canada, and the United Kingdom (8, 15–18), telephone triage nurses request ambulance dispatches or give a caller the information on appropriate hospitals based on the telephone triage results (19). Our software records data generated by the telephone triage such as gender, age group of the patient, duration of the telephone triage, chief complaint and associated signs, telephone triage results, and whether an ambulance was dispatched, or not.

Main Outcome

The main outcome of this study was unnecessary ambulance use. We defined the following cases as unnecessary ambulance use: "patients refuse transport to hospital," "there was no patient," "ambulance call was canceled during ambulance dispatch," "ambulance call was made as a result of mischief," and "patient was too drunk to be transported to hospital."

Statistical Analysis

Propensity Score Matching

The purpose of this study was to evaluate the effectiveness of an intervention in which people use telephone triage service and the nurses assess the urgency of symptoms and triage callers. However, since the telephone triage service was already in existence in Osaka, Japan, we used propensity score matching as the main statistical analysis in this study. We calculated a PS by fitting a logistic regression model to adjust for the 10 variables that existed before the use of the telephone triage service. The variables used to calculate a PS were age, sex, calendar year, month, day of the week, time of day, public holiday and weekend, reason for ambulance call, administrative districts, and location of occurrence. The time of day was classified in 1-h increments. Reason for ambulance call and location of occurrence were categorized according to the ambulance record in the OMFD (20). Administrative districts were classified into 24 areas defined by Osaka city. We performed one-to-one pair matching between cases for which an ambulance was dispatched via telephone triage service or not by nearest-neighbor matching without

Abbreviations: CI, confidence interval; EMS, emergency medical service; OMFD, Osaka Municipal Fire Department; OR, odds ratio; PS, propensity score; SMD, standardized mean difference; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

replacement, using calipers of width equal to 0.2 of the standard deviation mean difference (SMD) of the logit of the PS. Covariate balances before and after matching were checked by comparison of SMD. A SMD of <0.1 was considered to show a negligible imbalance between the two groups (21).

Other Statistical Analyses

To ensure the robustness of the analysis with PS matching model, we also analyzed with a multivariable logistic regression model and a regression model with PS as a covariate. The variables entered into the multivariable logistic regression model were the 10 variables used in the calculation of the PS, and telephone triage service. In addition, we divided the age groups into children (0–14 years old), adults (15–64 years old), and the elderly (65 years old and over) and assessed them in the same way. All tests were two-tailed, and *P* values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS ver 27.0J (IBM Corp. Armonk, NY).

RESULTS

Figure 1 shows patient flow in this study. The number of ambulance dispatches in Osaka city was 950,541 during the study period and we included 868,548 patients in this study. Among the cases included in this study, 8,828 (1.0%) used telephone triage services and 859,720 (99.0%) did not use this service.

Table 1 shows the characteristics of the cases before and after PS matching. In all cohort before the PS matching, patients using the telephone triage service were younger, more likely to call for an ambulance due to "acute disease," and less likely to call for an ambulance due to "traffic accident by car" and "other injury." Regarding location of occurrence, the proportion of "home" was high, followed by that of "public space" and "road, highway and railroad" in cases using the telephone triage service. In the PS matched cohort, 8,828 cases were selected from each group, and the balances of all covariates improved between the two groups after PS matching. The area under the curve in the logistic regression model for PS calculation was 0.808.

Table 2 shows the proportion of unnecessary ambulance use in all cohort and the PS-matched cohort. The number of unnecessary ambulance uses was 66,100 (7.6%) in all cohort. Of them, 330 patients (3.7%) used the telephone triage service and 65,770 patients (7.7%) did not. In the PS-matched cohort, the number of unnecessary ambulance uses was 982 (5.6%), in which 330 (3.7%) patients used the telephone triage service and 652 (7.7%) did not use the service. The use of the telephone triage service was inversely associated with the occurrence of unnecessary ambulance use in a PS matching model (crude OR 0.487, 95% CI 0.425–0.588). And, we also revealed the same results in a univariate logistic regression model (crude odds ratio [OR] 0.469, 95% confidence interval [CI] 0.420–0.523), multivariate logistic regression model (adjusted OR 0.453, 95%

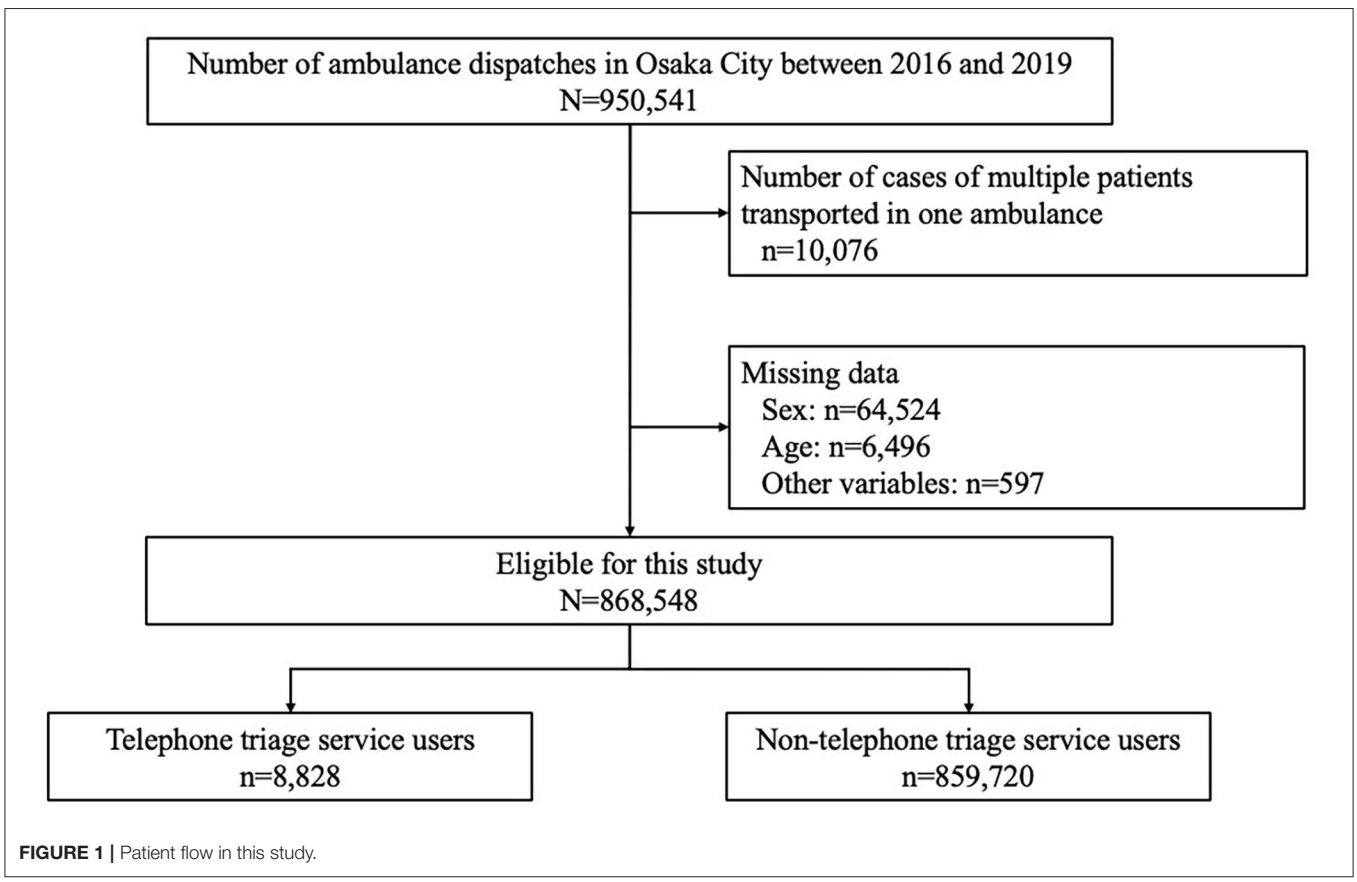

FIGURE 1 | Patient flow in this study.

TABLE 1 | Patient characteristics among all cohorts and the propensity score-matched cohort.

	All patients					Propensity score-matched patients				
	Telephone triage service users (*N* = 8,828)		Non-telephone triage service users (*N* = 859,720)		SMD	Telephone triage service users (*N* = 8,828)		Non-telephone triage service users (*N* = 8,828)		SMD
Age, mean (SD)	43.4	(27.9)	58.8	(25.2)	0.579	43.4	(27.9)	44.4	(28.1)	0.036
Male, *n* (%)	4,050	(45.9%)	4,60,719	(53.6%)	0.155	4,050	(45.9%)	4,080	(45.3%)	0.012
Year, *n* (%)										
2016	1,984	(22.5%)	2,06,494	(24.0%)	0.037	1,984	(22.5%)	1,992	(22.6%)	0.002
2017	2,108	(23.9%)	2,10,338	(24.5%)	0.014	2,108	(23.9%)	2,163	(24.5%)	0.015
2018	2,279	(25.8%)	2,21,608	(25.8%)	0.001	2,279	(25.8%)	2,293	(26.0%)	0.004
2019	2,457	(27.8%)	2,21,280	(25.7%)	0.047	2,457	(27.8%)	2,380	(27.0%)	0.020
Month, *n* (%)										
January	662	(7.5%)	77,720	(9.0%)	0.056	662	(7.5%)	689	(7.8%)	0.012
February	591	(6.7%)	67,522	(7.9%)	0.045	591	(6.7%)	616	(7.0%)	0.011
March	683	(7.7%)	70,418	(8.2%)	0.017	683	(7.7%)	677	(7.7%)	0.003
April	659	(7.5%)	67,459	(7.8%)	0.014	659	(7.5%)	649	(7.4%)	0.004
May	710	(8.0%)	68,659	(8.0%)	0.002	710	(8.0%)	692	(7.8%)	0.008
June	747	(8.5%)	68,116	(7.9%)	0.020	747	(8.5%)	756	(8.6%)	0.004
July	817	(9.3%)	78,565	(9.1%)	0.004	817	(9.3%)	816	(9.2%)	0.000
August	871	(9.9%)	77,091	(9.0%)	0.031	871	(9.9%)	861	(9.8%)	0.004
September	698	(7.9%)	67,728	(7.9%)	0.001	698	(7.9%)	731	(8.3%)	0.014
October	773	(8.8%)	70,049	(8.1%)	0.022	773	(8.8%)	755	(8.6%)	0.007
November	769	(8.7%)	69,166	(8.0%)	0.024	769	(8.7%)	769	(8.7%)	0.000
December	847	(9.6%)	77,227	(9.0%)	0.021	847	(9.6%)	817	(9.3%)	0.012
Day of the week, *n* (%)										
Sunday	1,606	(18.2%)	1,24,529	(14.5%)	0.100	1,606	(18.2%)	1,625	(18.4%)	0.006
Monday	1,231	(13.9%)	1,27,027	(14.8%)	0.024	1,231	(13.9%)	1,247	(14.1%)	0.005
Tuesday	1,205	(13.6%)	1,20,232	(14.0%)	0.010	1,205	(13.6%)	1,226	(13.9%)	0.007
Wednesday	1,131	(12.8%)	1,17,324	(13.6%)	0.025	1,131	(12.8%)	1,049	(11.9%)	0.028
Thursday	1,238	(14.0%)	1,19,240	(13.9%)	0.004	1,238	(14.0%)	1,302	(14.7%)	0.021
Friday	1,114	(12.6%)	1,24,556	(14.5%)	0.055	1,114	(12.6%)	1,082	(12.3%)	0.011
Saturday	1,303	(14.8%)	1,26,812	(14.8%)	0.000	1,303	(14.8%)	1,297	(14.7%)	0.002
Weekend and holiday, *n* (%)	3,368	(38.2%)	2,87,380	(33.4%)	0.099	3,368	(38.2%)	3,372	(38.2%)	0.001
Time of day, *n* (%)										
0:00–0:59	450	(5.1%)	28,110	(3.3%)	0.091	450	(5.1%)	454	(5.1%)	0.002
1:00–1:59	372	(4.2%)	23,342	(2.7%)	0.082	372	(4.2%)	368	(4.2%)	0.002
2:00–2:59	313	(3.5%)	20,045	(2.3%)	0.072	313	(3.5%)	337	(3.8%)	0.014
3:00–3:59	252	(2.9%)	17,869	(2.1%)	0.050	252	(2.9%)	269	(3.0%)	0.011
4:00–4:59	259	(2.9%)	16,768	(2.0%)	0.064	259	(2.9%)	242	(2.7%)	0.012
5:00–5:59	236	(2.7%)	18,046	(2.1%)	0.038	236	(2.7%)	256	(2.9%)	0.014
6:00–6:59	263	(3.0%)	21,590	(2.5%)	0.029	263	(3.0%)	288	(3.3%)	0.016
7:00–7:59	315	(3.6%)	27,742	(3.2%)	0.019	315	(3.6%)	317	(3.6%)	0.001
8:00–8:59	329	(3.7%)	38,031	(4.4%)	0.035	329	(3.7%)	348	(3.9%)	0.011
9:00–9:59	308	(3.5%)	47,811	(5.6%)	0.100	308	(3.5%)	301	(3.4%)	0.004
10:00–10:59	302	(3.4%)	48,772	(5.7%)	0.108	302	(3.4%)	279	(3.2%)	0.015
11:00–11:59	266	(3.0%)	46,558	(5.4%)	0.120	266	(3.0%)	281	(3.2%)	0.010
12:00–12:59	271	(3.1%)	45,401	(5.3%)	0.111	271	(3.1%)	272	(3.1%)	0.001
13:00–13:59	319	(3.6%)	45,249	(5.3%)	0.080	319	(3.6%)	318	(3.6%)	0.001
14:00–14:59	341	(3.9%)	42,737	(5.0%)	0.054	341	(3.9%)	323	(3.7%)	0.011
15:00–15:59	290	(3.3%)	42,179	(4.9%)	0.082	290	(3.3%)	301	(3.4%)	0.007
16:00–16:59	350	(4.0%)	42,785	(5.0%)	0.049	350	(4.0%)	366	(4.1%)	0.009
17:00–17:59	371	(4.2%)	45,166	(5.3%)	0.050	371	(4.2%)	328	(3.7%)	0.025

(Continued)

TABLE 1 | Continued

	All patients					Propensity score-matched patients				
	Telephone triage service users (*N* = 8,828)		Non-telephone triage service users (*N* = 859,720)		SMD	Telephone triage service users (*N* = 8,828)		Non-telephone triage service users (*N* = 8,828)		SMD
18:00–18:59	427	(4.8%)	45,268	(5.3%)	0.020	427	(4.8%)	451	(5.1%)	0.013
19:00–19:59	570	(6.5%)	43,637	(5.1%)	0.059	570	(6.5%)	567	(6.4%)	0.001
20:00–20:59	618	(7.0%)	42,163	(4.9%)	0.089	618	(7.0%)	594	(6.7%)	0.011
21:00–21:59	568	(6.4%)	39,908	(4.6%)	0.078	568	(6.4%)	556	(6.3%)	0.006
22:00–22:59	553	(6.3%)	36,890	(4.3%)	0.088	553	(6.3%)	532	(6.0%)	0.010
23:00–23:59	485	(5.5%)	33,553	(3.9%)	0.075	485	(5.5%)	480	(5.4%)	0.002
Reason for ambulance call										
Fire accident	3	(0.0%)	390	(0.0%)	0.006	3	(0.0%)	0	(0%)	0.026
Natural disaster	1	(0.0%)	197	(0.0%)	0.009	1	(0.0%)	0	(0%)	0.015
Water accident	0	(0%)	182	(0.0%)	0.021	0	(0%)	0	(0%)	-
Traffic accident by car	42	(0.5%)	54,089	(6.3%)	0.326	42	(0.5%)	58	(0.7%)	0.024
Traffic accident by ship	0	(0%)	2	(0.0%)	0.002	0	(0%)	0	(0%)	-
Traffic accident by aircraft	0	(0%)	3	(0.0%)	0.003	0	(0%)	0	(0%)	-
Injury due to industrial accident	17	(0.2%)	5,883	(0.7%)	0.074	17	(0.2%)	11	(0.1%)	0.017
Poisoning and acute disease due to industrial accident	1	(0.0%)	192	(0.0%)	0.008	1	(0.0%)	1	(0.0%)	0.000
Acute disease and injury during sports	19	(0.2%)	3,770	(0.4%)	0.039	19	(0.2%)	9	(0.1%)	0.028
Acute disease and injury while watching sports	0	(0%)	104	(0.0%)	0.016	0	(0%)	0	(0%)	-
Asphyxia	106	(1.2%)	3,205	(0.4%)	0.094	106	(1.2%)	87	(1.0%)	0.021
Gas poisoning not due to industrial accident and self-injury	1	(0.0%)	62	(0.0%)	0.004	1	(0.0%)	0	(0%)	0.015
Other injury	692	(7.8%)	1,34,762	(15.7%)	0.245	692	(7.8%)	708	(8.0%)	0.007
Assault	14	(0.2%)	8,968	(1.0%)	0.115	14	(0.2%)	15	(0.2%)	0.003
Self-induced drug abuse and gas poisoning	61	(0.7%)	4,216	(0.5%)	0.026	61	(0.7%)	64	(0.7%)	0.004
Self-induced injury	6	(0.1%)	3,241	(0.4%)	0.066	6	(0.1%)	9	(0.1%)	0.012
Acute disease	7,729	(87.6%)	5,82,349	(67.7%)	0.490	7,729	(87.6%)	7,690	(87.1%)	0.013
Gynecological disease including childbirth	136	(1.5%)	6,912	(0.8%)	0.068	136	(1.5%)	142	(1.6%)	0.005
Inter-hospital transfer	0	(0%)	50,844	(5.9%)	0.355	0	(0%)	33	(0.4%)	0.087
Other	0	(0%)	349	(0.0%)	0.028	0	(0%)	1	(0.0%)	0.015
Location of occurrence										
Home	7,951	(90.1%)	4,52,877	(52.7%)	0.908	7,951	(90.1%)	7,951	(90.1%)	0.000
Work place	184	(2.1%)	22,817	(2.7%)	0.037	184	(2.1%)	166	(1.9%)	0.015
Public place	371	(4.2%)	2,19,016	(25.5%)	0.627	371	(4.2%)	373	(4.2%)	0.001
Public transportation	14	(0.2%)	5,569	(0.6%)	0.077	14	(0.2%)	17	(0.2%)	0.008
Road, highway and railroad	244	(2.8%)	1,47,079	(17.1%)	0.494	244	(2.8%)	248	(2.8%)	0.003
Sea, pools and rivers	0	(0%)	364	(0.0%)	0.029	0	(0%)	0	(0%)	-
Other indoor areas	12	(0.1%)	1,914	(0.2%)	0.020	12	(0.1%)	10	(0.1%)	0.006
Other outdoor areas	52	(0.6%)	10,084	(1.2%)	0.063	52	(0.6%)	63	(0.7%)	0.015
Area										
Kita-ku	554	(6.3%)	63,250	(7.4%)	0.043	554	(6.3%)	551	(6.2%)	0.001
Miyakojima-ku	400	(4.5%)	28,896	(3.4%)	0.060	400	(4.5%)	375	(4.2%)	0.014
Fukushima-ku	211	(2.4%)	17,809	(2.1%)	0.022	211	(2.4%)	221	(2.5%)	0.007
Konohana-ku	176	(2.0%)	21,483	(2.5%)	0.034	176	(2.0%)	196	(2.2%)	0.016
Chuo-ku	480	(5.4%)	56,022	(6.5%)	0.046	480	(5.4%)	482	(5.5%)	0.001
Nishi-ku	329	(3.7%)	27,272	(3.2%)	0.030	329	(3.7%)	306	(3.5%)	0.014
Minato-ku	219	(2.5%)	24,726	(2.9%)	0.024	219	(2.5%)	205	(2.3%)	0.010

(Continued)

TABLE 1 | Continued

	All patients					Propensity score-matched patients				
	Telephone triage service users (*N* = 8,828)		Non-telephone triage service users (*N* = 859,720)		SMD	Telephone triage service users (*N* = 8,828)		Non-telephone triage service users (*N* = 8,828)		SMD
Taisho-ku	162	(1.8%)	20,269	(2.4%)	0.036	162	(1.8%)	177	(2.0%)	0.012
Tennnoji-ku	285	(3.2%)	23,565	(2.7%)	0.029	285	(3.2%)	266	(3.0%)	0.012
Naniwa-ku	277	(3.1%)	30,694	(3.6%)	0.024	277	(3.1%)	292	(3.3%)	0.010
Nishiyodogawa-ku	251	(2.8%)	26,474	(3.1%)	0.014	251	(2.8%)	261	(3.0%)	0.007
Yodogawa-ku	557	(6.3%)	50,467	(5.9%)	0.018	557	(6.3%)	554	(6.3%)	0.001
Higashiyodogawa-ku	480	(5.4%)	45,942	(5.3%)	0.004	480	(5.4%)	481	(5.4%)	0.000
Higashinari-ku	289	(3.3%)	21,231	(2.5%)	0.048	289	(3.3%)	276	(3.1%)	0.008
Ikuno-ku	343	(3.9%)	38,807	(4.5%)	0.031	343	(3.9%)	316	(3.6%)	0.016
Asahi-ku	265	(3.0%)	22,768	(2.6%)	0.021	265	(3.0%)	277	(3.1%)	0.008
Joto-ku	519	(5.9%)	39,133	(4.6%)	0.060	519	(5.9%)	544	(6.2%)	0.012
Tsurumi-ku	323	(3.7%)	25,075	(2.9%)	0.042	323	(3.7%)	317	(3.6%)	0.004
Abeno-ku	402	(4.6%)	28,112	(3.3%)	0.066	402	(4.6%)	396	(4.5%)	0.003
Suminoe-ku	436	(4.9%)	38,658	(4.5%)	0.021	436	(4.9%)	413	(4.7%)	0.012
Sumiyoshi-ku	497	(5.6%)	41,990	(4.9%)	0.033	497	(5.6%)	524	(5.9%)	0.013
Higashisumiyoshi-ku	433	(4.9%)	36,802	(4.3%)	0.030	433	(4.9%)	427	(4.8%)	0.003
Hirano-ku	654	(7.4%)	56,502	(6.6%)	0.033	654	(7.4%)	675	(7.6%)	0.009
Nishinari-ku	286	(3.2%)	73,558	(8.6%)	0.227	286	(3.2%)	296	(3.4%)	0.006
Outside Osaka City	0	(0%)	215	(0.0%)	0.022	0	(0%)	0	(0%)	-

EMS represents emergency medical service. SMD, standardized mean difference; SD, standard deviation; IQR, interquartile range.

TABLE 2 | Unnecessary ambulance use with or without telephone triage service.

	Total		Telephone triage service used		Telephone triage service not used		Crude OR (95% CI)		Adjusted OR (95% CI)	
All patients	(*N* = 868,548)		(*N* = 8,828)		(*N* = 859,720)					
Unnecessary ambulance use	66,100	(7.6%)	330	(3.7%)	65,770	(7.7%)				
Univariate logistic regression model							0.469	(0.420–0.523)	-	-
Multivariate logistic regression model*							-	-	0.453	(0.405–0.506)
Regression model with propensity score as covariate							-	-	0.514	(0.460–0.574)
Propensity score-matched patients	(*N* = 17,656)		(*N* = 8,828)		(*N* = 8828)					
Unnecessary ambulance use	982	(5.6%)	330	(3.7%)	652	(7.4%)	0.487	(0.425–0.588)	-	-

*OR represents odds ratio; CI, confidence interval. ORs were calculated for patients with vs. without telephone triage service. *Adjusted for age, sex, calendar year, month, day of the week, time zone, holiday including weekend, reason for ambulance call, administrative district, and accident location.*

CI 0.405–0.506), multivariate logistic regression model with PS as a covariate (adjusted OR 0.514, 95% CI 0.460–0.574).

Table 3 shows the proportion of unnecessary ambulance use in all cohort and PS-matched cohort among children. The proportions of unnecessary ambulance use were 3.3% (58/1,768) among the patients using the telephone triage service and 4.0% (2,103/53,097) among those not using the service. The crude OR was 0.725 (95% CI 0.513–1.024) in this PS-matched cohort.

Table 4 shows the proportion of unnecessary ambulance use in all cohort and PS-matched cohort among adults. The proportions of unnecessary ambulance use were 4.4% (198/4,468) among the patients using the telephone triage service and 11.1%

TABLE 3 | Unnecessary ambulance use with or without telephone triage service among children.

	Total		Telephone triage service used		Telephone triage service not used		Crude OR (95% CI)		Adjusted OR (95% CI)	
All patients	(*N* = 54,865)		(*N* = 1,768)		(*N* = 53,097)					
Unnecessary ambulance use	2,161	(3.9%)	58	(3.3%)	2,103	(4.0%)				
Univariate logistic regression model							0.822	(0.631–1.072)	-	-
Multivariate logistic regression model*							-	-	0.760	(0.581–0.995)
Regression model with propensity score as covariate							-	-	0.782	(0.599–1.022)
Propensity score-matched patients	(N = 3,536)		(N = 1,768)		(N = 1,768)					
Unnecessary ambulance use	137	(3.9%)	58	(3.3%)	79	(4.5%)	0.725	(0.513–1.024)	-	-

*OR represents odds ratio; CI, confidence interval. ORs were calculated for patients with vs. without telephone triage service. *Adjusted for age, sex, calendar year, month, day of the week, time zone, holiday including weekend, reason for ambulance call, administrative district, and accident location.*

TABLE 4 | Unnecessary ambulance use with or without telephone triage service among adults.

	Total		Telephone triage service used		Telephone triage service not used		Crude OR (95% CI)		Adjusted OR (95% CI)	
All patients	(*N* = 364,723)		(*N* = 4,468)		(*N* = 360,255)					
Unnecessary ambulance use	40,282	(11.0%)	198	(4.4%)	40,084	(11.1%)				
Univariate logistic regression model							0.370	(0.321–0.427)	-	-
Multivariate logistic regression model*							-	-	0.393	(0.340–0.455)
Regression model with propensity score as covariate							-	-	0.428	(0.371–0.494)
Propensity score-matched patients	(*N* = 8,936)		(*N* = 4,468)		(*N* = 4,468)					
Unnecessary ambulance use	652	(7.3%)	198	(4.4%)	454	(10.2%)	0.410	(0.345–0.487)	-	-

*OR represents odds ratio; CI, confidence interval. ORs were calculated for patients with vs. without telephone triage service. *Adjusted for age, sex, calendar year, month, day of the week, time zone, holiday including weekend, reason for ambulance call, administrative district, and accident location.*

(40,084/360,255) among those not using it. The crude OR was 0.410 (95% CI 0.345–0.487) in this PS-matched cohort.

Table 5 shows the proportion of unnecessary ambulance use in the total cohort and PS-matched cohort among the elderly. The proportions of unnecessary ambulance use were 2.9% (74/2,592) in the patients using the telephone triage service and 5.3% (23,583/446,368) in those not using the service. The crude OR was 0.639 (95% CI 0.474–0.860) in this PS-matched cohort.

DISCUSSION

In this study, we were able to statistically evaluate the effectiveness of telephone triage service already in use by the public using the statistical method with PS. As a result, it was revealed that the use of a telephone triage service was associated with a lower proportion of unnecessary ambulance use in a metropolitan area of Japan. In subgroup analysis by age group, although the telephone triage service was associated with a lower proportion of unnecessary ambulance use in adults and the elderly, the proportion of unnecessary ambulance use tended to be lower, but not statistically significantly so, in children. To the best of our knowledge, there is no study using population-based data to assess the impact of a telephone triage service for emergency patients on the EMS system, and the findings of this study may help to improve EMS systems around the world.

First, we found that the proportion of unnecessary ambulance use was lower in cases for which an ambulance was dispatched via telephone triage service than in cases without telephone triage service. In Japan, because calling for an ambulance is free of

TABLE 5 | Unnecessary ambulance use with or without telephone triage service among the elderly.

	Total		Telephone triage service used		Telephone triage service not used		Crude OR (95% CI)		Adjusted OR (95% CI)	
All patients	(*N* = 448,960)		(N = 2,592)		(*N* = 446,368)					
Unnecessary ambulance use	23,657	(5.3%)	74	(2.9%)	23,583	(5.3%)				
Univariate logistic regression model							0.527	(0.418–0.664)	-	-
Multivariate logistic regression model*							-	-	0.546	(0.432–0.689)
Regression model with propensity score as covariate							-	-	0.585	(0.464–0.737)
Propensity score-matched patients	(*N* = 5,182)		(*N* = 2,591)		(*N* = 2,591)					
Unnecessary ambulance use	188	(3.6%)	74	(2.9%)	114	(4.4%)	0.639	(0.474–0.860)	-	-

OR represents odds ratio; CI, confidence interval.

ORs were calculated for patients with vs. without telephone triage service.

**Adjusted for age, sex, calendar year, month, day of the week, time zone, holiday including weekend, reason for ambulance call, administrative district, and accident location.*

charge, it may be called for even in less urgent cases. Therefore, people may be calling for an ambulance even when they do not necessarily need it. Several previous studies have shown the effect of telephone triage in reducing emergency department visits and same-day visits to health care facilities (22–24). In an observational study by Hogenbirk et al. in Canada, telephone triage advice reduced caller intention to visit the emergency department, and the effect appears to be stronger in communities with a weak or no transport link than in urban areas (24). In contrast, Richards et al. reported that telephone triage in primary care increased both the workload of nurses and the number of out-of-hours visits and ambulance dispatches for accidents (25). Furthermore, Doctor et al. found that one-third of patients who visited emergency departments after telephone triage did not require referral to the emergency department (26). Thus, the effect of telephone triage services is controversial and may be related to differences in health care systems in each country. A previous study by Turbitt and Freed in Victoria, Australia reported a 20% awareness of telephone triage services among patients who visited emergency departments with non-urgent children (27). To make telephone triage service work, it is important to increase public awareness and to spread information on the effectiveness of the service. Thus, the present study is useful because we revealed the impact of telephone triage services on an EMS system. We showed that only 1% of ambulances were dispatched via telephone triage. In Japan, anyone can call 1-1-9 for free access to an ambulance. In other countries such as Australia, the telephone triage service is used to triage the call and then transfer it to the ambulance dispatch center (8, 10). To make telephone triage service more effective, it may be necessary not only to educate the public but also to change the social system for calling for an ambulance.

The use of a telephone triage service in the present study was associated with a lower rate of unnecessary ambulance use in adults and the elderly, but the rate was not statistically significantly lower in children. Several studies have reported higher rates of ambulance transport among the elderly visiting a emergency department (28, 29). Durant and Fahimi reported that older age, Medicare, Medicaid, and nighttime were associated with less urgent ambulance use (3). Elderly people with health anxiety may call for an ambulance when they are worried about their health, even if it is not an emergency situation. Telephone triage services relieve the anxiety of such callers by determining the urgency of their symptoms and conditions using software with a triage protocol. As a result, few callers with such health concerns called for an ambulance via the telephone triage service, and the proportion of unnecessary ambulance use was probably lower among them. Thus, the telephone triage service may help to make the EMS system more efficient. However, the effect of the telephone triage service was smaller in children than in adults and the elderly, and the reason for this result was unclear. In many cases, parents or guardians are the ones who call for an ambulance for a suddenly sick or injured child, and when they do, they may strongly prefer to transport the child to a medical facility and see a doctor. This may explain why the proportion of unnecessary ambulance use was low even in cases for which the telephone triage service was not used, and why the effect of the service was not statistically significant in pediatric patients. In the PS-matched cohort, the proportion of unnecessary ambulance use was 7.4% in cases without telephone triage service vs. 3.7% in cases with telephone triage service. In a previous study, the cost of an ambulance call in Japan was estimated to be 45,000 yen (400 dollars) (30). If the proportion of unnecessary ambulance use was to be reduced to 3.7% by the use of telephone triage service, this would result in an annual saving of 407,925,000 yen (US$3.7 million) in Osaka city. As the annual cost of telephone triage service in Osaka city is ∼200,000,000 yen (US$1.8 million) (31), this would result in a reduction of ∼200,000,000 yen (US$1.8 million). In this way, the telephone triage service is an essential tool in the EMS system as it may

reduce the cost of government through effective dispatching of ambulances.

In recent years, infrastructures of centralized personal health records (PHR) are being built using blockchain technology (32). If such a PHR infrastructure can be built and used for telephone triage, it would lead to the realization of tailor-made telephone triage service based on patient's factors such as past medical history and medication history. In addition, it may also be possible to evaluate the outcome of cases in which patients are not urgent and visit a clinic on their own without ambulance transport as a result of telephone triage, as well as to track long-term prognosis such as return to work after rehabilitation. Thus, as the PHR infrastructure is built up, there will be scope for further enhancement of the telephone triage service in the future.

Limitations

This study has some limitations. First, we did not assess the patient's family structure or the relationship between the patient and the person who called for an ambulance, such as a family member, colleague, or bystander. Second, we did not assess the impact of using the telephone triage service on patient outcomes. We are currently studying this and will publish our findings in the future. Third, the outcomes were unknown in the cases for which an ambulance was not dispatched as a result of telephone triage. In addition, this study did not include a detailed cost analysis, but we plan to evaluate quality-adjusted life years and incremental cost-effectiveness ratios. Finally, as this is an observational study, there may be unknown confounding factors.

CONCLUSION

In observational studies, bias of background factors is a problem when comparing outcomes between groups, and this study made an effort to minimize those biases as much as possible by using the statistical analysis with PS. As a result, we found that the use of the telephone triage service in Osaka city reduced unnecessary ambulance use, especially among adults and the elderly in this study.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings of this study are available from the OMFD but restrictions apply to the availability of these data, which were used under the personal information protection ordinance of Osaka City, and so are not publicly available. Requests to access these datasets should be directed to Osaka Municipal Fire Department (in Japanese) https://www.city.osaka.lg.jp/shobo/page/0000052526.html.

ETHICS STATEMENT

This study was approved by the Ethics Committees of the Osaka Graduate School of Medicine (Approval No: 16070). The requirement to obtain patient consent to participate was waived because the data were anonymized.

AUTHOR CONTRIBUTIONS

YK analyzed the data and wrote the first draft of this manuscript. TK reviewed all statistical analyses and critically revised this manuscript. SN, HH, and RD interpreted the data and critically revised this manuscript. ST and JT did data cleaning and provided the data for analysis. YM, TS, and YN supervised the interpretation of the data and critically revised this manuscript. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW
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Effectiveness of Early Warning Scores for Early Severity Assessment in Outpatient Emergency Care: A Systematic Review

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Background and Objectives: Patient assessment and possible deterioration prediction are a healthcare priority. Increasing demand for outpatient emergency care services requires the implementation of simple, quick, and effective systems of patient evaluation and stratification. The purpose of this review is to identify the most effective Early Warning Score (EWS) for the early detection of the risk of complications when screening emergency outpatients for a potentially serious condition.

Materials and Methods: Systematic review of the bibliography made in 2022. Scientific articles in Spanish and English were collected from the databases and search engines of Pubmed, Cochrane, and Dialnet, which were published between 2017 and 2021 about EWSs and their capacity to predict complications.

Results: For analysis eleven articles were selected. Eight dealt with the application of different early warning scores in outpatient situations, concluding that all the scoring systems they studied were applicable. Three evaluated the predictive ability of various scoring systems and found no significant differences in their results. The eight articles evaluated the suitability of NEWS/NEWS2 to outpatient conditions and concluded it was the most suitable in pre-hospital emergency settings.

Conclusions: The early warning scores that were studied can be applied at the pre-hospital level, as they can predict patient mortality in the short term (24 or 48 h) and support clinical patient evaluation and medical decision making. Among them, NEWS2 is the most suitable for screening potentially deteriorating medical emergency outpatients.

Keywords: emergency medicine, Emergency Medical Service (EMS), medicine, emergency care, scale

INTRODUCTION

Scientific evidence shows that patient deterioration can be predicted from 6 to 24 h in advance (1–3). Sudden changes in heart rate, arterial systolic blood pressure, respiratory rate, temperature, oxygen saturation, or level of consciousness, happen moments before the clinical deterioration of the patient (1). Given this evidence, the European Resuscitation Council published Guidelines in 2021 requiring hospitals to have an early warning scoring system in place to identify patients whose state of health may suffer imminent deterioration. Correct evaluation of patients through these systems should be complemented with specially trained personnel qualified to provide a prompt response, reducing mortality from cardiac arrest in hospitalized patients (4, 5). A significant number of preventable mortality cases could be avoided by implementing early warning scores and quick response systems, as previous patient deterioration is not detected in up to 31% of preventable inpatient mortality (6).

The target is identical when it comes to outpatients; however, there are very limited diagnostic tools available in this setting. A rating scale easy to apply would help clinics make better decisions when determining patients with a higher deterioration chance, resulting in better care and the prevention of complications (7).

There are numerous early warning scores of the risk of complications, up to 100, used in different countries since the late 90's to evaluate patient conditions (8). They carry out early detection of clinical deterioration, thus facilitating the activation and intervention of response teams and enabling a quick transfer to intensive care units, which improves the prognosis and chances of survival (9). These tools measure a set of physiological parameters that are objectively standardized and validated (**Annex 1**) (3, 10).

Assessing the patient is an essential step in early deterioration detection both in and out of the hospital. A correct assessment will achieve two goals. First, providing the patient with a greater level of care, thus preventing deterioration, and promoting an earlier recovery. The second goal is a direct consequence of the first, i.e. greater system efficiency, since reducing morbidity will lead to shorter hospital stays and less health spending, while always guaranteeing the best quality of care (1, 4, 5).

Spain's growing demand for healthcare by using the 112/061 emergency numbers (11) requires the establishment of an effective and validated care prioritization system, which should fulfill two purposes. One is to facilitate the decision-making process of the doctors and nurses of the Coordination Centers for Urgencies and Emergencies assessing the conditions of patients calling from home and mobilizing the appropriate health care resources in the shortest time possible (7, 12–14). The other purpose is to facilitate the decision-making process in the triage and assignment of patients arriving at the hospital, providing a comprehensive and reliable assessment that will expedite the care process, reducing waiting time and promoting quick patient care (15–17). Non-invasive pre-hospital monitoring of the parameters needed to establish the use of validated rating is simple, and it could improve the chances of early patient deterioration detection (1, 7, 12).

The above will affect the quality of care and the satisfaction level of the population receiving it (10, 18) as far as perceived patient safety (10, 13, 16, 19). These two concepts are most important in current health management for improving healthcare effectiveness and efficiency.

Regarding the recommendation established by the European Resuscitation Council Guidelines (2021), it seems relevant to examine the literature on the properties of the scales currently used, both in and out-of-hospital. This article will make available to healthcare professionals a document that summarizes the most current evidence and will enable clinical decision making. It will be particularly relevant for optimizing the detection and management of potentially severe patients. In addition, it will be innovative for outpatients, as the available evidence in this setting is more limited.

Based on the above, the aim of this study is to identify the most effective early detection score of the risk of complications in potentially serious medical conditions of emergency outpatients.

MATERIALS AND METHODS

Method: systematic review of the literature created from September 2021 to January 2022 according to PRISMA statement guidelines (20).

Review and search: five of the authors participated in the search of literature available in Spanish and English from 2017 to 2021 relating to early warning scores applied to the assessment of adult patients (≥18 years), using Pubmed, Cochrane, and Dialnet search engines and data.

Inclusion criteria: cross-sectional descriptive scientific articles, case series, randomized clinical essays, and systematic reviews including bibliography generally showing the use of validated scores; articles referring to the predictive ability of various scores.

Exclusion criteria: articles collecting editorials, clinical notes, and letters to the editor; articles referring to care for pregnant women; articles about scores designed to assess the severity of specific conditions (sepsis, trauma, covid); articles on early warning scores with a single parameter.

Search strategy: a researcher did the initial search; two authors carried out the selection of articles independently; subsequently, the studies selected by each of the reviewers were reassessed for inclusion, with a third reviewer resolving discrepancies. Two authors selected the variables and evaluated the quality of the articles selected, while a third researcher handled any discrepancies. The search was completed by "reverse search"; the 2021 Executive Summary and Guidelines of the European Resuscitation Council were consulted, together with the 2020 Cardiopulmonary Resuscitation Guidelines of the American Heart Association, in addition to the Spanish legislation in force and Ministry of Health statistics portal, to contextualize the current situation in Spain. The following natural language terms were searched: Early warning scores, Pre-hospital setting, Deteriorating patients. The following MeSH terms were searched: Early warning score, Emergency Medical Services. Logical relations were established between these terms using the Boolean operators AND to narrow the search, and OR to broaden it. The

TABLE 1 | Search strategy.

Database	Search strategy	Results	Selected	References
Pubmed	((“Emergency Medical Services”[Mesh]) AND (early warning score [MeSH Terms])	58	7	(13–16, 19, 21)
	(“Early Warning Score”[Mesh] AND (prehospital setting)	13	5	(9, 12–14, 19)
	“Early Warning Score”[Mesh] AND (meta-analysis [Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (systematicreview[Filter])	16	1	(17)
	Early Warning Score AND ((y_5[Filter]) AND (meta-analysis [Filter] OR systematicreview[Filter]) AND (alladult[Filter]))	6	0	
	Early warning score AND deteriorating patients AND pre-hospital setting	5	1	(15)
Dialnet	Early warning scores	19	2	(10, 12)
Cochrane	“Early warning score” AND “prehospital setting”	17	0	

TABLE 2 | Research question in PICO format.

Patient	Intervention	Comparison	Result
Potentially serious patients	Assessment using most effective early warning score in outpatient setting	Effectiveness of different early warning scores	Early deterioration detection

search strategy (**Table 1**) was based on the following research question raised in the review and made using the format PICO (22): What is the most effective early warning score in outpatient settings to assess patients with potentially serious conditions and early deterioration detection? (**Table 2**).

Quality assessment: CASPe (23) critical appraisal and STROBE (24) statement checklists were used, according to the type of study evaluated. Compliance with 70% of the items evaluated was established as the minimum quality criterion to include an article in the study.

Data collection: a previously designed template was used to collect the following data: author, year, type of study, methodological quality (checklist and result obtained), population/sample, early warning score(s) evaluated in the study, score effectiveness, and outpatient validation. Score effectiveness was defined as the capacity to predict patient mortality within 24 or 48 h.

Research variables: short-term prediction capacity (24 or 48 h); pre-hospital application of early warning scores; early warning scores validated for the outpatient setting.

Identification of articles: 132 articles were identified initially (Pubmed 98, Dialnet 19 and Cochrane 17). Upon the removal of duplicates (15 articles) and those not conforming with the established criteria (59 articles), we proceeded with reading the title summary of the remaining (58 articles). After checking inclusion and exclusion criteria, 16 studies were finally selected for eligibility assessment. After a critical review, 5 articles were eliminated, 3 of them because they did not meet the quality criteria, and the other 2 because they did not satisfy the inclusion criteria in the end. After a detailed process of localization, choice, and inclusion, 11 articles were selected for inclusion in the study. This process is summarized in the annexed flowchart (**Figure 1**).

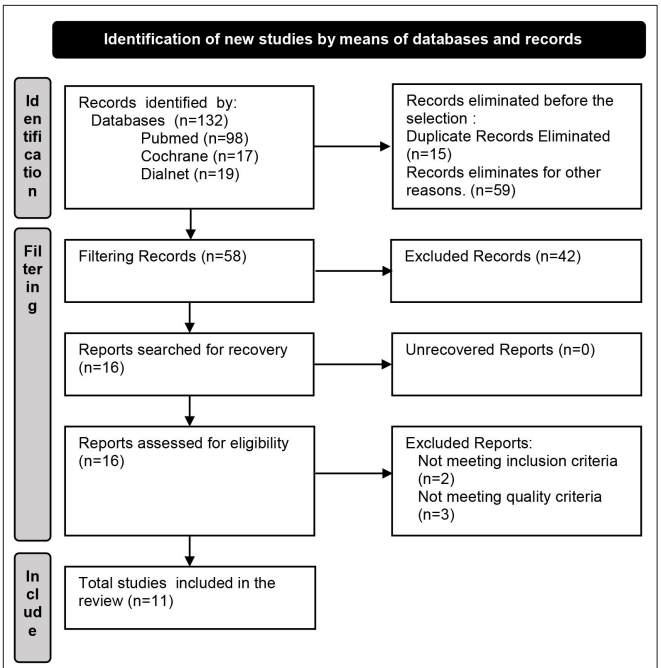

FIGURE 1 | Flowchart.

RESULTS

Eleven studies were included in the review, published between 2017 and 2021. Three of these were observational studies (9, 12, 13), three were systematic reviews (10, 15, 17), one featured a

meta-analysis (15), and the remaining five were cohort studies (7, 14, 16, 19, 21), two of them prospective (7, 16) and three retrospective (14, 19, 21). As for the country of publication, five were published in Spain (7, 9, 10, 12, 13), two in the United Kingdom (15, 17), two in Finland (19, 21), one in Australia (16), and one in Japan (14). Eight of the articles focused on the application of early warning scores at the outpatient level (7, 9, 12–15, 19, 21). The most cited were the National Early Warning Score (NEWS) and its 2017 update NEWS2, referred to in all eleven studies. Five articles cited the VitalPAC Early Warning Score (ViEWS) (9, 10, 13, 16) or Prehospital VitalPAC Early Warning Score (PhViEWS) (15), and the Modified Early Warning Score (MEWS) (9, 10, 13, 15, 16); other scores were only cited in three or fewer articles. The main goal of eight of the studies was to assess the short-term prediction ability of various scores as far as mortality within 24 or 48 h (9, 10, 12, 13, 16, 17, 19, 21). The goal of two of the articles was to determine deterioration prediction capacity (7, 15). Three had the main purpose of determining both short-term mortality and deterioration prediction capacity (10, 16, 17). Three sought to determine the applicability of early warning scores in a pre-hospital setting (9, 13, 14).

Short-Term Prediction Ability (24 or 48 h)

After analyzing prediction capacity, we concluded that most of the EWS scores were good or excellent predictors of short-term mortality (9, 16). The ViEWS score stood out as the most predictive, followed by NEWS and AbViEWS (9). One of the studies (17) specified that NEWS was better to identify patients at a greater risk of mortality within 24 h. The authors emphasized the importance of complying with the EWS application protocols and activating Quick Response Teams to obtain the highest effectiveness from these systems. Two of the articles analyzed (7, 19) agreed in affirming that NEWS (NEWS2) showed a high short-term mortality prediction ability. Two studies considered the possibility of increasing NEWS prediction capacity by adding the capillary glucose figure or that of lactate serum. One of them compared the prediction capacity of NEWS and NEWS-gluc (capillary glucose determination added), establishing that the NEWS-gluc calculation had a slightly higher ability to identify risk than NEWS (21). The other assessed whether the addition of lactate serum to pre-hospital NEWS might improve early mortality prediction, reaching the conclusion that there were no significant differences between NEWS and NEWS-L in this regard (12).

Pre-hospital Application of Early Warning Scores

The scores NEWS2, MEWS, ViEWS, TREWS, WPSS (Worthing Physiological Scoring System, MREMS (Modified Rapid Emergency Medicine Score) (25), and PI (Prehospital Index) (26) are clinical tools that can help decision making at a critical time and whose use would help standardize early deterioration detection in the outpatient setting (13). The EWS, MEWS, HEWS, ViEWS, SEWS, and NEWS2 systems are suitable for pre-hospital use due to their ease of application in this setting (9); however, patient assessment using these scores should never replace objective clinic evaluation, as the two should be complementary (9, 15). In the United Kingdom, the NEWS score is widely used in the pre-hospital setting (15).

After testing the validity of NEWS2, MEWS, ViEWS, WPSS (Worthing Physiological Scoring System), TREWS, MREMS (Modified Rapid Emergency Medicine Score), and PI (Prehospital Index) in the pre-hospital setting, it was established that there were no significant differences between them (13). The use of NEWS2 was justified because it is a tool validated for pre-hospital use that offers advantages from the clinical point of view (it evaluates the supply of oxygen to the patient), and multiple studies confirm its usefulness. Applied to the outpatient setting, NEWS2 was established to be an excellent predictor of which patients have a greater possibility of mortality in the short term, while also emphasizing the importance of facilitating patient assessment considering the limited resources available in this setting (7, 14, 19). The calculation of NEWS-gluc (21) and NEWS-L (12) at the outpatient level is possible if both parameters are easily determined and managed even in outpatient locations.

Early Warning Scores Validated for the Outpatient Setting

Our 11-article review observed the use of 25 early warning scores: EWS, NEWS2 (NEWS), NEWS-gluc, NEWS2-L, MEWS, PMEWS, MEWS GCS, ViEWS, PhViEWS, AbViEWS, WPPS, TREWS, REMS, MREMS, PI, HEWS, SWES, PRS, NzNEWS, RAPS, P. GOODACRE, P. GROARKE, GAP, VSS, and VSG. We were able to verify the validation at the pre-hospital level for seven of them: NEWS2 (NEWS), MEWS, ViEWS, WPPS, TREWS, MREMS, and PI.

The analysis of the 11 articles (**Table 3**) selected shows that the NEWS2 score (NEWS) is a useful, simple, and effective tool applicable in any setting, for both systematic patient assessment and pre-hospital healthcare (7, 12, 13, 27).

DISCUSSION

The present study allowed us to summarize the existing information on healthcare use of early warning scores of the risk of complications. These scores were initially designed for hospital use. There is a great deal of scientific evidence on the suitability of EWS to detect patients with greater chances of short-term mortality (24 or 48 h) (16). This motivated an investigation on the convenience of applying these scores to other healthcare levels, including pre-hospital (9, 13, 16). The growing demand for healthcare through Emergency Medical Services (EMS)—the Ministry of Health statistics portal recorded 9,084,399 requests in 2020—led to the mobilization of 4,611,404 aid resources by land and air (6). As a result, it is essential to establish a rating system to help identify users who need immediate attention. It is paramount to identify the early warning score of the risk of complications considered the most effective for screening potentially serious conditions in emergency service patients.

Our study shows that many of the early warning scores of risk are reliable tools; most of them obtained results showing a great ability to predict short-term mortality, including in pre-hospital

TABLE 3 | Results.

Author, Year	Population / sample	Plan	Score assessed	Score effectiveness (24 h)[1] (48 h)[2]	Outpatient validation	Methodological quality
Martín-Rodríguez et al. (7)	2,335	Multicentre prospective cohort study	NEWS 2	AUC 0.862[1]	SI	9/11***
Martín-Rodríguez et al. (9)	349	Prospective longitudinal observational study	EWS MEWS HEWS ViEWS SWES NEWS2	AUC 0.885[2] AUC 0.848[2] AUC 0.890[2] AUC 0.894[2] AUC 0.884[2] AUC 0.896[2]	SI SI SI SI SI SI	17/22*
Arévalo-Buitrago et al. (10)	165,580	Systematic review and meta-analysis	NEWS2 MEWS REMS TREWS SEWS ViEWS	AUC 0.883[1]; 0.8867[2] – – – – –	SI SI - - SI SI	9/10**
Martín-Rodríguez et al. (12)	707	Observational, prospective, and longitudinal study	NEWS2-L NEWS 2	AUC 0.91[2] AUC 0.90[2]	- SI	20/22*
Martín-Rodriguez et al. (13)	3,273	Prospective multicentre observational cohort study	NEWS 2 MEWS ViEWS WPPS TREWS MREMS PI	AUC 0.861[1]; 0.86[2] AUC 0.848[1]; 0.846[2] AUC 0.873[1]; 0.862[2] AUC 0.861[1]; 0.864[2] AUC 0.871[1]; 0.868[2] AUC 0.867[1]; 0.864[2] AUC 0.831[1]; 0.827[2]	SI SI SI SI SI SI	10/11***
Takuro Endo et al. (14)	2,847	Observational retrospective cohort study	NEWS	AUC 0.90[1]	SI	9/11***
Rita Patel et al. (15)	157,878	Systematic review	NEWS MEWS PMEWS PRS NzNEWS PhNEWS	- - - - - -	SI SI - - - -	9/10**
William Spencer et al. (16)	690	Prospective cohort study	RAPS MEWS MEWS GCS REMS P. GOODACRE WPS P. GROARKE ViEWS/AbViEWS GAP VSS NEWS VSG	AUC 0.81[2] AUC 0.91[2] AUC 0.91[2] AUC 0.83[2] AUC 0.78[2] AUC 0.90[2] AUC 0.89[2] AUC 0.96[2]/0.95[2] AUC 0.81[2] AUC 0.86[2] AUC 0.95[2] AUC 0.67[2]	SI - - - - - SI - - SI -	10/11***
Nicola Credland et al. (17)		Systematic review	NEWS/NEWS2	AUC 0.894	SI	9/10**
Pirneskoski, et al. (19)	35,800	Retrospective cohort study	NEWS	AUC 0.840[1]	SI	10/11***
Vihonen et al. (21)	27,141	Retrospective cohort study	NEWS-gluc NEWS	AUC 0.851[1] AUC 0.844[1]	- SI	9/11***

**STROBE statement checklist of essential points that should be described when publishing observational studies. **CASPe critical appraisal checklist to help understand a systematic review. ***CASPe critical appraisal checklist to help understand a cohort study.*

settings (14). They are quick and easy to apply, which is very important in outpatient settings, where the available time and adverse conditions of patient care are usually unfavorable and the need to make quick decisions with very limited information is a constant in the day-to-day work of the staff in these services. Therefore, we can agree that most of the EWS scores allow us to identify critical and potentially critical patients and assess the seriousness of their clinical situation, which facilitates the decision-making process and quick response of care teams (15). They are also easily applicable in outpatient settings,

although not all of them are validated for this use (9, 13). The standardization of an EMS patient assessment system will be useful to administrative management, insofar as it will facilitate decisions for either hospital admission or home care, choosing the best device to transfer a patient (7, 19), or making a pre-alert call to the hospital (9), in addition to making clinical decisions regarding the most appropriate patient treatment (9, 15). Most importantly, it is a tool that will provide objectivity in decision-making, thus ensuring that the intervention on the patient is the same regardless of the professional providing the care. The application of the scale would lead all professionals to make the same decision regarding the need for transfer and the most appropriate treatment.

The Spanish emergency system, through the 112 and 061 services, is equipped with the personnel (physicians, nurses, emergency health technicians and teleoperators, announcers and administrative assistants) and mobile devices (A1, B and C ambulances, emergency air teams, rapid intervention vehicles and special disaster vehicles) (11) necessary to implement an assessment system using an early assessment scale.

This study was also intended to establish which of the early warning scores of risk is more effective for the detection of mortality within 24 or 48 h. Data comparison evidenced that all the scores have great prediction capacity for short-term death, as shown by the AUC figures being between 0.90 (CI 95% 0.87–0.93) for NEWS at 24 h recorded in the study of Takuro Endo et al. (14) and 0.831 (CI 95% 0.78–0.87) for Prehospital Index at 24 h recorded in the study by Martín-Rodríguez et al. (13). From this we can determine that the most effective score to predict the chance of mortality within 24 h is NEWS/NEWS2, and that Prehospital Index is the least effective.

As for the 48 h mortality prediction period, the situation is similar, NEWS2-L and NEWS2 show the highest ability in the study by Martín-Rodríguez et al. (12), followed by MEWS according to another study by Martín-Rodríguez et al. (9), PI being the lowest in this case too, Martín-Rodríguez et al. (13). The effectiveness of early warning scores is a fact, as they all have great ability to identify patients with a high probability of deterioration (7, 10, 15–17).

There are no differences based on which to choose a score over another, as they have all been shown to have excellent predictive value for short-term complication, based on they all show a good adequacy. Nonetheless, we can propose NEWS/NEWS2 as the most suitable for general EMS use, because it is a simple and useful tool, validated for outpatient application, and indicated by scientific evidence for all levels of healthcare (7, 12, 13, 27). There are also two analytical parameters, easily determinable with portable analysers, which can support NEWS prediction; these are the readings of capillary blood glucose (21) and lactic acid in venous blood (12), which are easy to obtain and can be applied to outpatient care. In any case, in addition to determining the warning score, it is essential to carry out a clinical assessment of the patient (15), as these two procedures are complementary and objective and to be used together to determine clinical deterioration and the best response to the actual situation of the patient (13).

Even though all the scores we reviewed measure basically the same physiological parameters and have a very similar prediction capacity, the NEWS score is the most applied, which could be the reason why it was one of the first to be implemented at a national level, in this case the United Kingdom, in all health care areas. It provides some clinical advantages, such as assessing oxygen administration to the patient, and it is endorsed by the Royal College of Physicians (13). Specifically, the parameters that need to be recorded for the calculation of the NEWS 2 scale are respiratory rate, oxygen saturation, oxygen supply to the patient, heart rate, systolic blood pressure, temperature and neurological status by means of a simple assessment: AVDN.

The effectiveness of early detection scales is a fact, all of them having a great capacity to identify patients with a high probability of deterioration. In addition, they also appear to be effective in detecting patients who are not at risk of deterioration.

Limitations

The main limitation is that there are a multitude of references for the use of early warning scores to predict serious risk in hospital settings, since they were specifically designed for this purpose. There is increasingly more research about their application in emergency and outpatient medicine, but it is still scarce. Finding bibliography on the validation of different scores for outpatient use turned out to be very complicated.

CONCLUSIONS

The NEWS2 score is the most widespread and recognized in the world. This is because it is simple and easy to use by the whole clinical staff, including validation, effectiveness, and availability anywhere, and useful in triage and systematic patient assessment. Although we do recommend it, all the scores analyzed show great effectiveness for short-term (24 or 48 h) mortality prediction. The application of EWS in outpatient medicine can help standardize patient assessment and detect early clinical deterioration, this being one of the main EMS objectives, as it will lead to better quality patient care with lower morbidity and mortality. The scores suitable for prehospital use should be easy to calculate and not require large diagnostic means, as the latter are not available in outpatient care. Nonetheless, these scores can never replace clinical patient assessment, as the two must complement each other. NEWS/NEWS2 is the most effective validated early warning score in outpatient settings as far as the risk of complications and the detection of potentially serious emergency care situations. It is one of the first scores to have been implemented, easy to calculate and manage, and validated in both in-hospital and outpatient settings.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

AB-E, VG-C, and RJ-V: conception or design of the work and final approval of the version to be published. AB-E

and IS-A: data collection. VG-C, MC-H, and EM-S: data analysis, interpretation, and drafting the article. PM-M, AS-G, MG-L, JS-G, and JG-C: critical revision of the article. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.894906/full#supplementary-material

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Identification of biomarkers and the mechanisms of multiple trauma complicated with sepsis using metabolomics

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Sepsis after trauma increases the risk of mortality rate for patients in intensive care unit (ICUs). Currently, it is difficult to predict outcomes in individual patients with sepsis due to the complexity of causative pathogens and the lack of specific treatment. This study aimed to identify metabolomic biomarkers in patients with multiple trauma and those with multiple trauma accompanied with sepsis. Therefore, the metabolic profiles of healthy persons designated as normal controls (NC), multiple trauma patients (MT), and multiple trauma complicated with sepsis (MTS) (30 cases in each group) were analyzed with ultra-high performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-Q-TOF/MS)-based untargeted plasma metabolomics using collected plasma samples. The differential metabolites were enriched in amino acid metabolism, lipid metabolism, glycometabolism and nucleotide metabolism. Then, nine potential biomarkers, namely, acrylic acid, 5-amino-3-oxohexanoate, 3b-hydroxy-5-cholenoic acid, cytidine, succinic acid semialdehyde, PE [P-18:1(9Z)/16:1(9Z)], sphinganine, uracil, and uridine, were found to be correlated with clinical variables and validated using receiver operating characteristic (ROC) curves. Finally, the three potential biomarkers succinic acid semialdehyde, uracil and uridine were validated and can be applied in the clinical diagnosis of multiple traumas complicated with sepsis.

KEYWORDS

biomarkers, multiple trauma, sepsis, metabolomics, mechanisms

Introduction

Trauma is one of the leading causes of morbidity and mortality among all age populations worldwide (1, 2). Multiple trauma is common injury at two or more anatomical sites caused by a single consistent injury factor. Besides the health status, multiple trauma can trigger a complex cascade of posttraumatic events, including massive secretion of proinflammatory cytokines, an imbalance between the early systemic inflammatory response, later compensatory anti-inflammatory response, and

even multiple organ failure, which are closely correlated with the outcomes of victims (3). Sepsis is a major cause of mortality in critically ill patients, especially patients with multiple trauma. Sepsis is a life-threatening condition caused by the body's extreme response to infection. It causes nearly six million deaths worldwide annually (4). Multiple trauma also causes sepsis. The trauma-induced sepsis is the leading cause of a high mortality rate in intensive care units (ICUs). Moreover, sepsis associated with multiple organ dysfunction syndrome is the primary cause of late posttraumatic mortality, accounting for up to 50% (5, 6). Although various advanced technologies, such as bundled early goal-directed therapy, have been used to sepsis, sepsis prognosis is still poor (7, 8). Furthermore, the high mortality associated with sepsis is partially due to the lack of an effective approach to predict sepsis outcomes. It is difficult to diagnose multiple trauma-induced sepsis because the hypermetabolic baseline and the explosive inflammatory immune response mask the clinical signs and symptoms of sepsis (9, 10). Therefore, it is necessary to determine promising biomarkers for patients with multiple trauma without sepsis to estimate the individual risk profile and prevent sepsis development.

Previous diagnostic definitions and manifestations of sepsis, including Glasgow or sequential organ failure assessment (SOFA) scores, have been performed based on sepsis 3.0 due to the substantial heterogeneity of clinical syndrome (11). The laboratory testing of sepsis is currently based on the related factors of acute immune response caused by host reactants in serum. C-reactive protein and procalcitonin have been widely used in clinics for infection diagnosis and sepsis progression prediction (12). Metabolite lactate has been standardized for indications of sepsis and septic shock. Furthermore, studies have shown that the proinflammatory cytokines interleukin-6 and tumor necrosis factor-alpha can be used as markers to diagnose sepsis (13, 14). Although patient blood culture is recommended for diagnosing the etiologic agent of sepsis, sepsis cannot be detected in most patients due to the low abundance of microorganisms in the bloodstream or because the organisms cannot be proliferated in conventional culture medium (15). However, these biomarkers are universal and non-specific in sepsis. Besides, the difficulty of early sepsis diagnosis and the limited knowledge of the molecular mechanism of sepsis development limits the timely treatment of sepsis (16). Therefore, specific biomarkers for sepsis diagnosis should be detected to help differentiate between the various factors and conditions associated with sepsis.

Omics technologies can identify biomarkers by detecting biochemical changes associated with the gene expression at the transcription and translation levels and metabolites in the overall biological state (17). Metabolomics is widely used to assess all metabolites contained in an organism. For instance, genome, transcriptome or proteome changes can be reflected in the metabolome as alterations of metabolite concentration (18). As a result, metabolomics can identify novel and potential metabolite markers and explore molecular mechanisms in various diseases, including sepsis, through blood detection. Metabolomics technology can also globally evaluate the totality of endogenous metabolites in the body of sepsis patients and reflect gene function and enzyme activity (19). However, metabolomics can be used to quantitatively distinguish patients with sepsis from healthy individuals by analyzing several low molecular weight compounds, such as amino acids, fatty acids, nucleotides and their derivatives, which are important in diagnosis and pathogenesis (20). However, clinical studies on sepsis metabonomics have not identified any specific biomarkers for multiple injuries-induced sepsis.

This study used untargeted metabolomics based on ultrahigh-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-Q-TOF/MS) to screen several metabolites in plasma samples of multiple trauma complicated with sepsis (MTS). A computational bioinformatics analysis was then used to obtain numerous significantly different metabolites. The metabolites were further analyzed based on the clinical data and characteristics of patients to obtain a set of potential metabolites that can be used in the clinical diagnosis and detection of MTS.

Materials and methods

Patients

This study was carried out in line with the Declaration of Helsinki and approved by the Ethics Committee of the General Hospital of Ningxia Medical University (No. 2020-34). All patients provided written informed consent. For ICU patients and those with serious multiple traumas, consents were provided by their legal guardians. Plasma samples were obtained from 30 patients with multiple trauma (MT) and 30 patients with multiple trauma complicated with sepsis (MTS) who were admitted in the outpatient room of the emergency department between 2016 and 2019. In addition, 30 samples were obtained from healthy normal individuals (NC, aged from 30 to 50) from the Healthy Examination Center of the General Hospital of Ningxia Medical University. All healthy volunteers were fully informed of the study details and agreed to participate in the investigation, and also provided written informed consent. Patients with MT or MTS were enrolled according to Sepsis-3 definition., complete basic information of patients was obtained. Plasma samples were collected within 1 h of hospitalization and before antibiotic treatment (21). Sequential Organ Failure Assessment (SOFA) score and Glasgow score were calculated to assess sepsis severity, and the scores were confirmed by two pathologists. Serum biochemical information of patients was obtained from the hospital database.

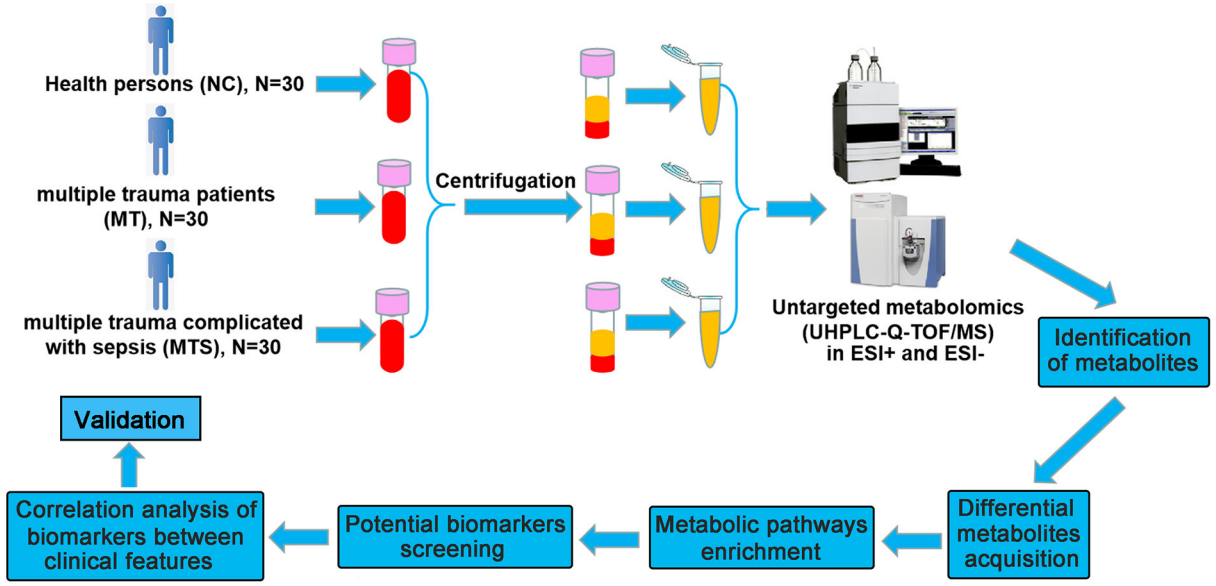

FIGURE 1
Schematic workflow for the experimental approach using untargeted metabolomics. The plasma were collected from NC, MT and MTS groups for metabolomics profiling using untargeted metabolomics. Quantitative information is extracted from MS data and identification based on database, and the metabolic pathways of differential metabolites were enriched and the potential biomarkers were further obtained, subsequently, the availability was predicted and the correlations between potential biomarkers and clinical characteristics were analyzed.

Preparation of plasma samples and extraction of metabolites

Plasma samples were collected from NC, MT, and MTS groups (30 patients for each group). The plasma samples were stored at −80°C and thawed at 4°C before LC-MS/MS analysis. Briefly, 200 μL of the extraction solution composed of acetonitrile/methanol (1:1, v/v) and isotopically labeled internal standard was added to 50 μL of each plasma sample, and mixed by vortexing for 30 s. It was sonicated for 10 min, and incubated for 1 h at −40°C. After centrifugation at 4°C and 12,000 g for 15 min, the supernatant was collected into a fresh glass vial for subsequent analysis. To ensure credibility of analysis, a bulk quality control (QC) sample was prepared by mixing equal volume aliquots and used for monitoring LC/MS response and calibrating data.

LC-MS/MS analysis

Untargeted metabolite profile of plasma samples was performed using an ultra-high-performance liquid chromatography (UHPLC) system (Vanquish, Thermo Fisher Scientific) coupled to a Q Exactive HFX mass spectrometer (Orbitrap MS, Thermo). Flow phase solution A: acetonitrile/water (60:40, v/v); flow phase solution B: acetonitrile/water (90:10, v/v), two flow phase solutions contain 10 mmol/L ammonium formate and 0.1% methanoic acid at final concentration. Then, a series of gradient solution B and solution A were eluted as follows: 95% solution B for 0.5 min, 70% solution B for 5 min, 50% solution B for 8 min, 40% solution B for 9 min, 70% solution A for 9 min and 95% solution A for 12 min. A mass spectrometer (Q Exactive HFX) was used to acquire MS/MS spectra data under the control of the acquisition software (Xcalibur, version 4.1, Thermo). Full scan MS spectra were continuously analyzed using the software. The parameters of electrospray used as the ionization (ESI) source conditions were as follows: sheath gas flow rate of 50 Arb, Aux gas flow rate of 10 Arb, capillary temperature of 320°C, full MS resolution of 60,000, MS/MS resolution of 7,500, collision energy of 10/30/60 in NCE mode, and spray voltage of 3.5 kV (positive model, ESI+) or −3.2 kV (negative model, ESI-) (22).

Validation of candidate metabolites

To validate the applicability of the candidate metabolites, the ultrahigh-performance liquid chromatography–tandem mass spectrometer (UHPLC-MS/MS) was employed to quantitatively measure the candidate metabolites in the plasma of another 20 cases (10 cases in MT and MTs groups, respectively). The chromatographic separation was accomplished on an Agilent 1,290 Infinity II series UHPLC System (Agilent Technologies, California, USA), equipped with a Waters ACQUITY UPLC

TABLE 1 The basic information and clinical characteristics of multiple trauma with sepsis and multiple trauma without sepsis.

Characteristics	Variables			
	All patients ($n = 60$)	Multiple trauma (MT, $n = 30$)	Multiple trauma with sepsis (MTS, $n = 30$)	P value (MT *vs.* MTS)
Male gender, *n* (%)	45 (75%)	22 (73%)	23 (77%)	1.0000
Age, years	40 (31 to 52)	35 (26 to 46)	44.5 (35.75 to 59.75)	0.0071**
Length of stay in the ICU, days	0 (0 to 1)	0 (0 to 0)	0 (0 to 4.25)	0.5729
SOFA score, points	0 (0 to 2)	0 (0 to 2)	2 (1 to 6)	0.0061**
Length of stay in hospital, days	16 (9.5 to 29.5)	23.5 (10.75 to 38.75)	21 (11 to 34)	0.1150
Glasgow score, points	15 (11 to 15)	15 (15 to 15)	12 (7.75 to 15)	0.0007**
Leukocyte count, $\times 10^9$/L	14.74 (12 to 20.85)	14.74 (11.14 to 18.02)	15.47 (11.99 to 21.95)	0.4362
Neutrophil count, $\times 10^9$/L	12.91 (9.58 to 17.95)	12.91 (9.675 to 14.19)	13.41 (9.497 to 19.42)	0.2077
Platelets, $\times 10^9$/L	183 (149 to 256)	183 (142.5 to 257)	189.5 (154.5 to 256.3)	0.4280
Total bilirubin, μmol/L	12.7 (9.1 to 23.3)	15.5 (9.45 to 22.95)	10.55 (8.65 to 24.83)	0.7753
Creatinine, mg/dL	62.6 (54.6 to 75.9)	64.9 (56.2 to 79.05)	62.5 (52.78 to 68.23)	0.2844
Oxygenation index, mmHg	268.6 (209.7 to 385)	271.2 (219.7 to 385.7)	257 (181.3 to 389.6)	0.3334

Data are expressed as medians and 25th to 75th percentiles or with frequencies and percentages. P value is statistically significant when <0.01 and those values are marked with an **. ICU, intensive care unit; SOFA, sequential organ failure assessment.

BEH Amide column (100 × 2.1 mm, 1.7 μm, Waters, USA). The mobile phase A was 1% formic acid with 20 mM ammonium formate in water, and phase B was 1% formic acid with 20 mM ammonium formate in acetonitrile. The column temperature and autosampler temperature were maintained at 35 and 4°C, respectively. The multiple reaction monitoring parameters of the target analytes are controlled by flowing injection of the standard solution of a single analyte.

Data preprocessing and annotation

The raw data of peak were converted to mzXML format and detected by R package based on XCMS (version 3.2). A data matrix consisting of retention time (RT), Mass-to-charge ratio (m/z) values, and peak intensity was established by preprocessing. After discarding the data of QC samples, monoisotopic peaks were subjected to subsequent statistical analyses. Metabolites were identified and annotated using HMDB, METLIN, and MoNA databases, developed by Biotree Technology Co. Ltd. (Shanghai, China) (23). A schematic workflow of the study is shown in Figure 1.

Statistical analysis

All statistical analyses were carried out using MetaboAnalyst 2.0 (http://www.metaboanalyst.ca). Principal component analysis (PCA, 95% confidence interval) was performed to visualize the distribution of sample groups and unsupervised multivariate statistical analysis. Orthogonal projections to latent structures-discriminate analysis (OPLS-DA) were performed as a supervised method to visualize group separation and identify significantly changed metabolites. In cross-validation and permutation tests, the OPLS-DA models were used according to multiple correlation coefficients (R2) and cross-validated R2 (Q2) value by 7-fold cross validation and 200 permutations. The principal component was obtained based on the importance of the projection (VIP) value determined using OPLS-DA analysis. Metabolites with VIP>1 and $P < 0.05$ (ANOVA) were considered significant differential metabolites among the groups. Pathway enrichment analysis was performed using KEGG (http://www.genome.jp/kegg/) and HMDB (http://www.hmdb.ca) databases (24, 25). Correlation analysis of metabolites and receiver operating characteristic (ROC) curves were drawn using GraphPad Prism 6.0. $P < 0.05$ was considered statistically significant.

Results

Patient demographics and clinical characteristics

This study enrolled 30 multiple trauma patients (MT) and 30 multiple trauma with sepsis (MTS) patients. The clinical characteristics of the patients are shown in Table 1. Forty-five patients (75%), including 22 MT patients and 23 MTS patients, were males. This showed that gender in MT and MTS groups has no difference ($P = 1.0000$). The median ages of the MT and MTS groups were 35 years (25th to 75th percentile, 26

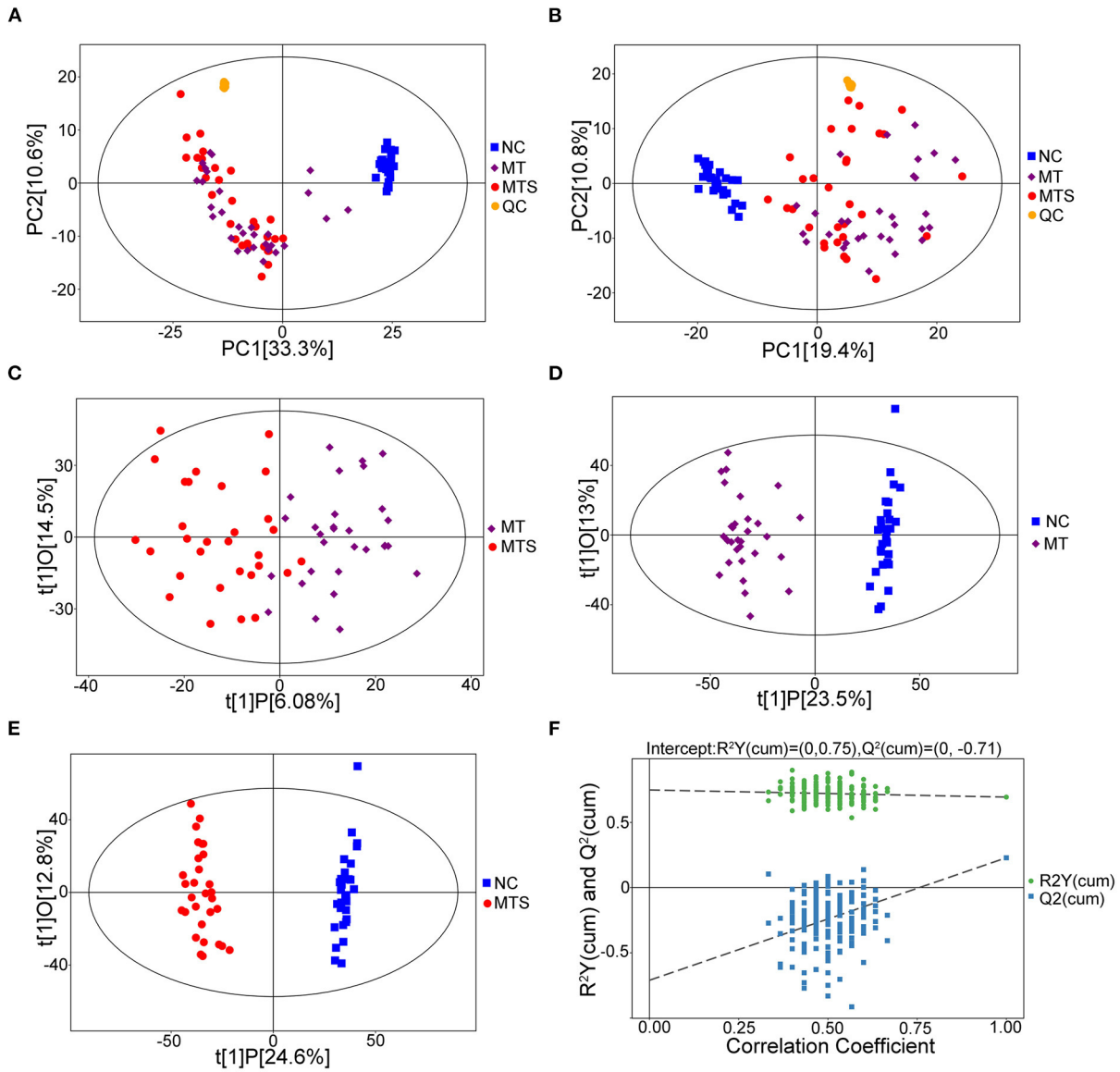

FIGURE 2
Metabolic profiles of plasma samples of NC, MT and MTS. **(A)** PCA score plots of the samples derived from the metabolite profiles in the ESI+ model, QC: quality control. **(B)** PCA score plots of the samples derived from the metabolite profiles in the ESI- model. **(C)** OPLS-DA score scatter plots of plasma samples of MTS *vs*. MT derived from the metabolite profiles in the ESI+ model. **(D)** OPLS-DA score scatter plots of plasma samples of MT *vs*. NC derived from the metabolite profiles in the ESI+ model. **(E)** OPLS-DA score scatter plots of plasma samples of MTS *vs*. NC derived from the metabolite profiles in the ESI+ model. **(F)** Permutation test of the OPLS-DA model for MTS *vs*. MT in the ESI+ model. $N = 30$ in each group. **(A–F)** were drawn by R version 4.0.2.

to 46 years) and 44.5 years (25th to 75th percentile, 35.75 to 59.75 years), respectively. This showed the patient's age in MT and MTS groups has a significant difference ($P = 0.0071$). Although the MTS patients stayed in the ICU for more days than the MT patients, the median and P values were not different between the two groups. The MTS patients were more severe and had a significantly higher SOFA score (MTS: median; 2 points and 25th to 75th percentile; 1–6 points) than the MT group (MT: median; 0 points and 25th−75th percentile; 0–2 points) ($P = 0.0061$). The MTS patients also had a significantly lower Glasgow score (MTS: median; 12 points and 25th−75th percentile; 7.75–15 points) than the MT patients (MT: median; 15 points and 25th−75th percentile; 15–15 points) ($P = 0.0007$). The results indicated that the SOFA score and the Glasgow score could be quickly distinguish patients with MT and MTS in clinical. Furthermore, the median length of hospital stay [21

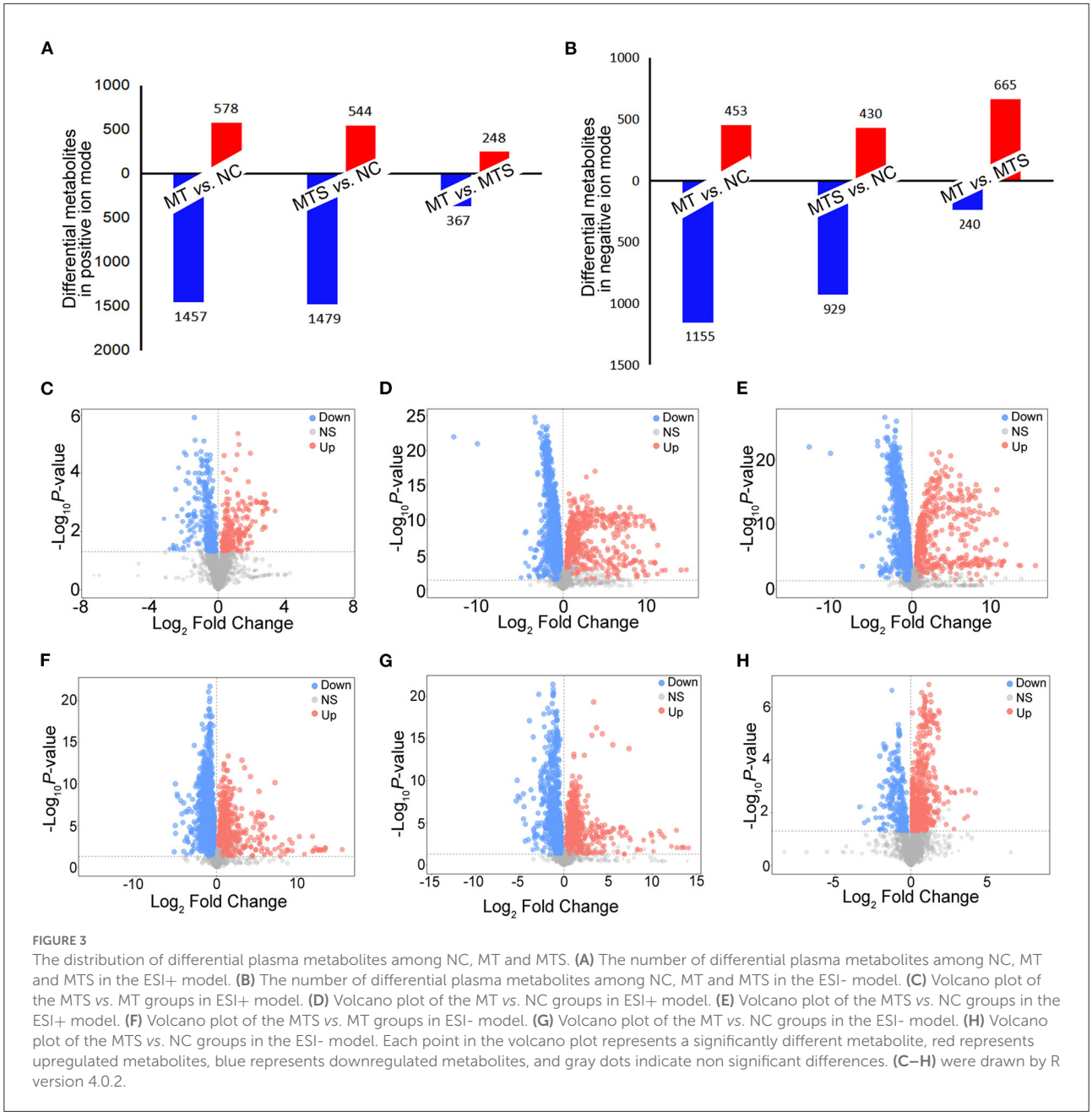

FIGURE 3
The distribution of differential plasma metabolites among NC, MT and MTS. **(A)** The number of differential plasma metabolites among NC, MT and MTS in the ESI+ model. **(B)** The number of differential plasma metabolites among NC, MT and MTS in the ESI- model. **(C)** Volcano plot of the MTS *vs*. MT groups in ESI+ model. **(D)** Volcano plot of the MT *vs*. NC groups in ESI+ model. **(E)** Volcano plot of the MTS *vs*. NC groups in the ESI+ model. **(F)** Volcano plot of the MTS *vs*. MT groups in ESI- model. **(G)** Volcano plot of the MT *vs*. NC groups in the ESI- model. **(H)** Volcano plot of the MTS *vs*. NC groups in the ESI- model. Each point in the volcano plot represents a significantly different metabolite, red represents upregulated metabolites, blue represents downregulated metabolites, and gray dots indicate non significant differences. **(C–H)** were drawn by R version 4.0.2.

(15–17, 19, 21–40) *vs*. 23.5 (10.75–38.75), $P = 0.1150$], leukocyte count [15.47 (11.99–21.95) *vs*. 14.74 (11.14–18.02), $P = 0.4362$], neutrophil count [13.41 (9.497–19.42) *vs*. 12.91 (9.675–14.19), $P = 0.2077$], platelets [189.5 (154.5–256.3) *vs*. 183 (142.5–257), $P = 0.4280$], total bilirubin [10.55 (8.65–24.83) *vs*. 15.5 (9.45–22.95), $P = 0.7753$], creatinine [62.5 (52.78–68.23) *vs*. 64.9 (56.2–79.05), $P = 0.2844$], and oxygenation index [257 (181.3–389.6) *vs*. 271.2 (219.7–385.7), $P = 0.3334$] were not significantly different between the MTS and MT groups. Therefore, these results suggested that the age, SOFA score and Glasgow score may be related to the incidence of MTS.

Assessment of metabolic profiles

This study used untargeted metabolomics to assess the relationship between plasma metabolome and MTS. The UHPLC/MS profile of plasma samples for MTS, MT and NC in positive (ESI+) and negative (ESI-) modes are shown in Figure 2. A total of 5,168 peaks and 1,434 metabolites were identified and quantified in the ESI+ model, while 4,078 peaks and 847 metabolites were identified and quantified in the ESI- model. These compounds were annotated based on internal libraries and reference standards. The

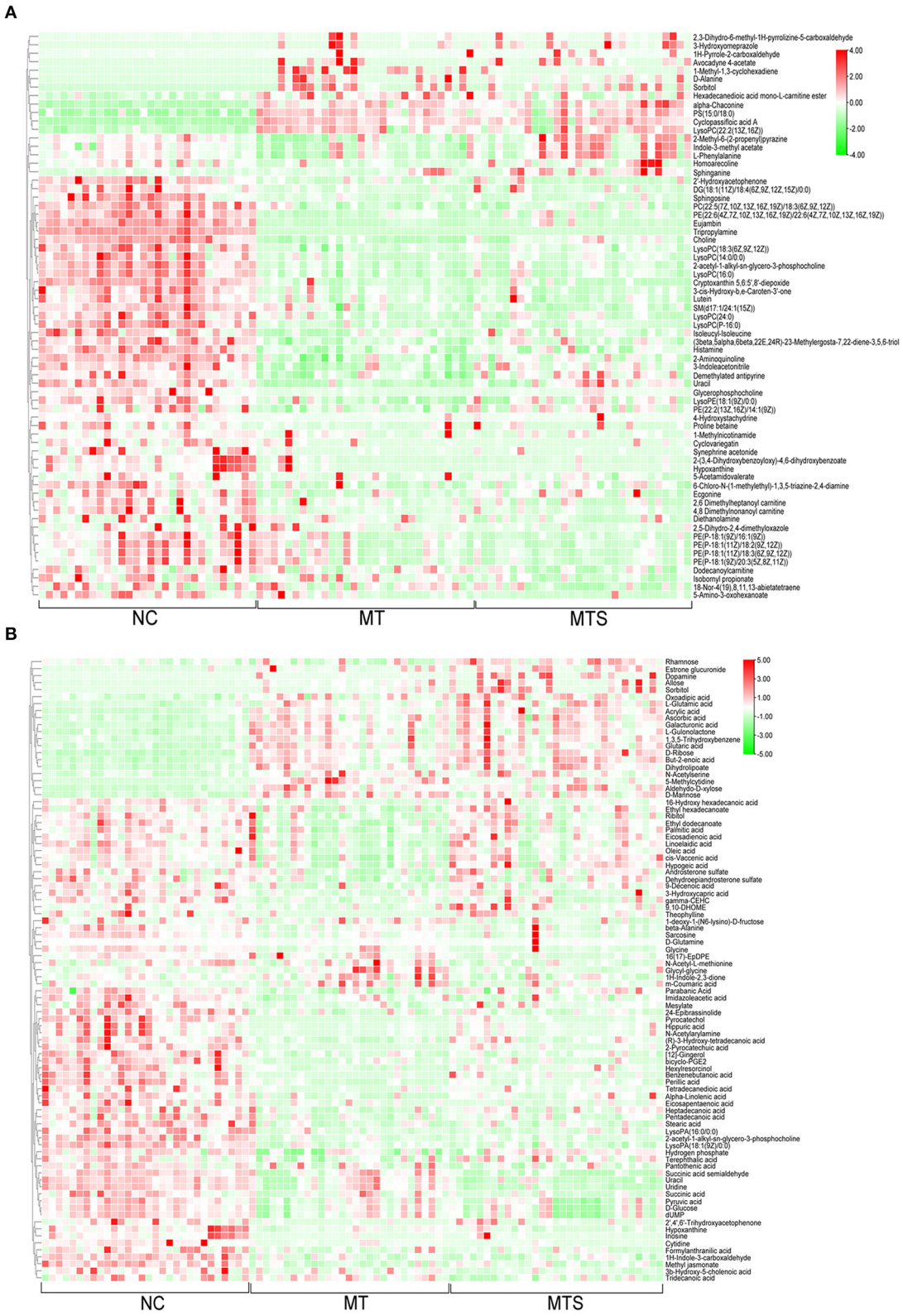

FIGURE 4
The hierarchical clustering heat map of metabolites from plasma of NC, MT and MTS groups in the ESI+ mode **(A)** and in the ESI- mode **(B)**. **(A,B)** were drawn by R version 4.0.2.

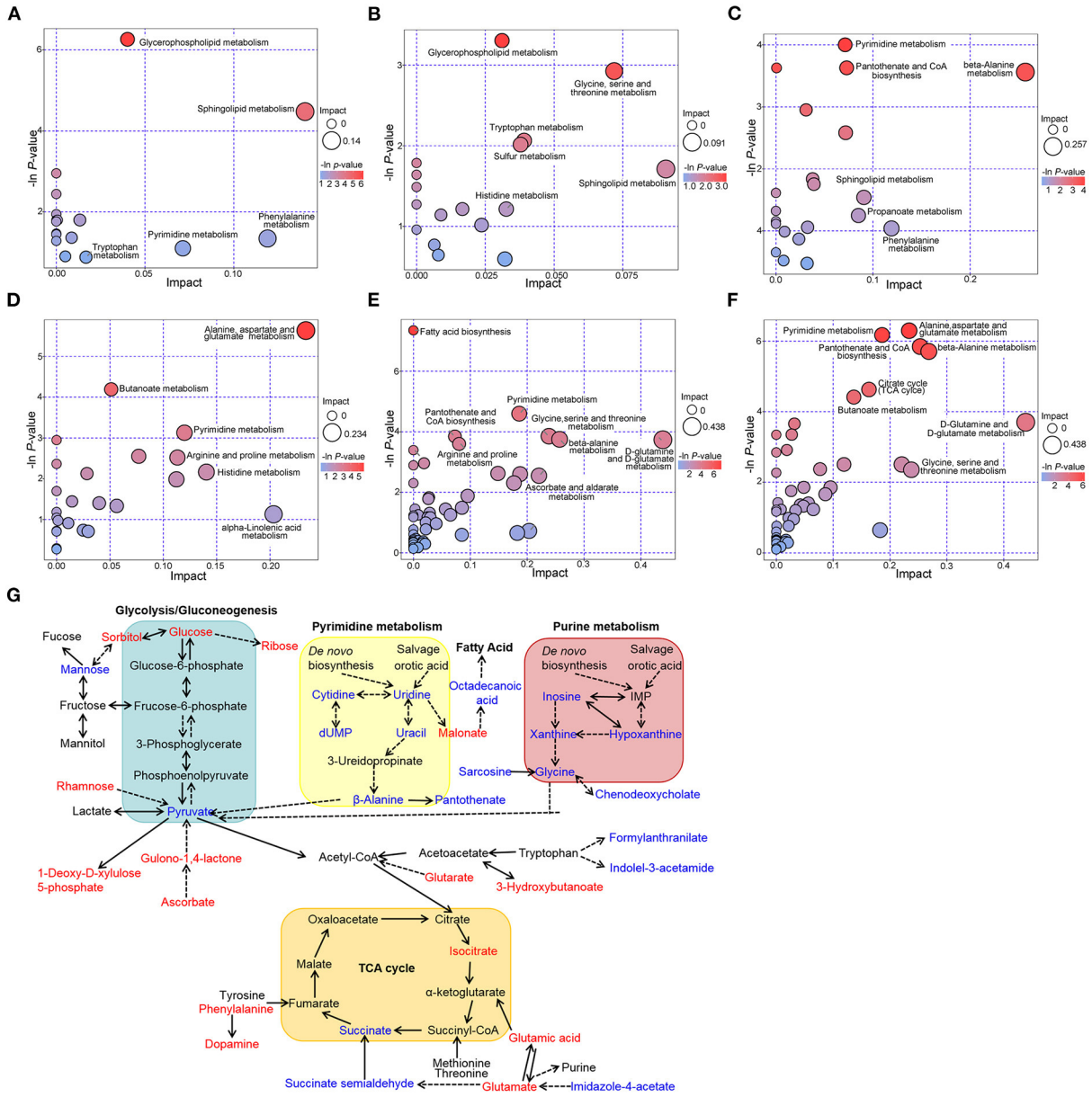

FIGURE 5
Metabolic pathways among NC, MT and MTS groups. Bubble diagram of the metabolic pathways of MTS *vs*. MT **(A)**, MT *vs*. NC **(B)**, and MTS *vs*. NC **(C)** in the ESI+ model. Bubble diagram of the metabolic pathways of MTS *vs*. MT **(D)**, MT *vs*. NC **(E)** and MTS *vs*. NC **(F)** in the ESI- model. The −ln(p) values from the pathway enrichment analysis are indicated on the horizontal axis, and impact values are indicated on the vertical axis. The colors and sizes of the shapes represent the effects of the pairwise comparison, and the larger red shapes indicate a greater effect on the pathway. **(G)** Schematic overview of the metabolites with plasma levels significantly altered in multiple trauma complicated with sepsis. Metabolites with increased levels are in red and those with decreased levels are in blue; Solid lines denote direct reactions; dotted lines denote indirect reactions; arrowhead indicates direction of the reaction; double arrowhead indicates direction of the reversible reactions. **(A–F)** were drawn by R version 4.0.2.

PCA score plot showed the NC, MT and MTS groups had different metabolic profiles. The ESI+ and ESI- models are shown in Figures 2A,B, respectively. The pairwise comparisons in the ESI+ and ESI− models is shown in Supplementary Figure 1. The orthogonal projections to latent structures discriminant analysis (OPLS-DA) were used to further assess the tendency of metabolite classification among the three groups. The OPLS-DA score plots of the MT *vs*. MTS groups (Figure 2C), NC *vs*. MT groups (Figure 2D), and NC *vs*. MTS groups (Figure 2E) in the ESI+ model

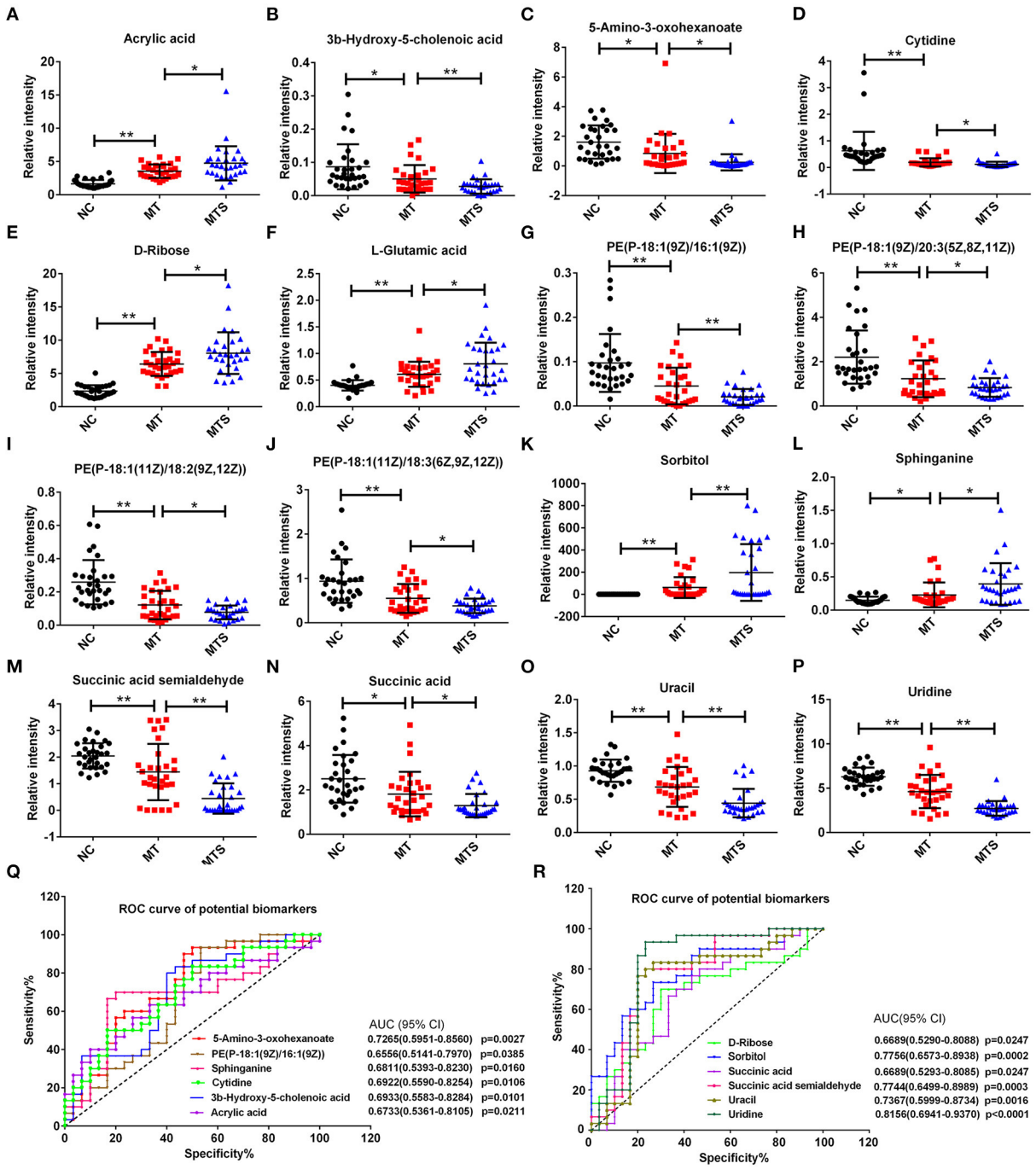

FIGURE 6
Scatter and trend plot of 16 potential biomarkers in the ESI+ and ESI- models. The scatter and trend plot of acrylic acid **(A)**, 3b-hydroxy-5-cholenoic acid **(B)**, 5-amino-3-oxohexanoate **(C)**, cytidine **(D)**, D-ribose **(E)**, L-glutamic acid **(F)**, PE [P-18:1(9Z)/16:1(9Z)] **(G)**, PE [P-18:1(9Z)/20:3(5Z,8Z,11Z)] **(H)**, PE [P-18:1(11Z)/18:2(9Z,12Z)] **(I)**, PE [P-18:1(11Z)/18:3(6Z,9Z,12Z)] **(J)**, sorbitol **(K)**, sphinganine **(L)**, succinic acid semialdehyde **(M)**, succinic acid **(N)**, uracil **(O)**, and uridine **(P)**, and the ordinate was the relative intensity of metabolite. **(Q,R)** Receiver operator curve (ROC) analysis of the random forest model combining 12 biomarkers ($P < 0.05$) to diagnose MTS in the validation data. $^{*}P < 0.05$, $^{**}P < 0.01$.

suggested that the metabolites were reliable based on the differences between the groups. The OPLS-DA score plots of the MT *vs.* MTS groups (Supplementary Figure 2A), NC *vs.* MT groups (Supplementary Figure 2B), and NC *vs.* MTS groups (Supplementary Figure 2C) in the ESI- model also showed that the metabolites were reliable based on differences

between the groups. Additionally, a random permutations test comparison between MT and MTS groups (ESI+) was performed to verify the validity and robustness of the OPLS-DA model. The negative corresponding Q2 value was used for the validation of the metabolic profiles (Figure 2F). Similarly, the comparison between the MT and MTS groups in the ESI- was valid (Supplementary Figure 2D).

Differential metabolites obtained from the plasma of MTS patients

This study used a pairwise comparison to screen the differential metabolites. The significantly differential metabolites were identified based on the criteria of variable importance of the projection (VIP) values >1.0 and *P* values < 0.05. A total of 1,457 metabolites were downregulated, and 578 were upregulated in the MT *vs*. NC, 1,479 metabolites were downregulated, and 544 were upregulated in the MTS *vs*. NC group, and 367 metabolites were downregulated, and 248 were upregulated in the MTS *vs*. NC group in the ESI+ model (Figure 3A). The volcano plots are shown in Figures 3C–E. A total of 1,155 metabolites were downregulated, and 453 were upregulated in the MT *vs*. NC group, 929 metabolites were downregulated, and 430 were upregulated in the MTS *vs*. NC group, and 240 metabolites were downregulated and 665 were upregulated in the MTS *vs*. NC group in the ESI- model (Figure 3B). The volcano plots are shown in Figures 3F–H.

Detection and identification of differential metabolites

One-way ANOVA was used to compare all data in NC, MT and MTS groups based on the criteria of VIP values >1.0. The critical *P* value was set to 0.05 for significantly differential metabolites. A total of 156 significant plasma metabolites (67 in the ESI+ model and 89 in the ESI- model) were obtained (Supplementary Table 1). This study also conducted tentative identification of these metabolites and their corresponding concentration fold change analyses. Positive and negative fold changes represented upregulation and downregulation within comparative groups, respectively. A greater fold change of metabolites between pairwise comparisons and metabolites may be a better biomarker. The profiles of hierarchical clustering analysis were then visualized to assess the global overview of all the significantly differential metabolites in the ESI+ (Figure 4A) and ESI- models (Figure 4B).

Pathway analysis of differential metabolites

The enrichment analysis was conducted using the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database to investigate the metabolites related to the metabolic pathways and physiological changes in the plasma of MTS patients. In the ESI+ model, glycerophospholipid, sphingolipid, tryptophan, pyrimidine, and phenylalanine metabolism pathways were affected in the MT *vs*. MTS group (Figure 5A); glycerophospholipid, glycine, serine, threonine, tryptophan, sulfur, sphingolipid, and histidine metabolism pathways were affected in the MT *vs*. NC group (Figure 5B); and pyrimidine, pantothenate and CoA biosynthesis, beta-alanine, sphingolipid, propanoate, and phenylalanine metabolism pathways were affected in the MTS *vs*. NC group (Figure 5C). In the ESI- model, alanine, aspartate, glutamate, butanoate, pyrimidine, arginine, proline, histidine, and alpha-linolenic acid metabolism pathways were affected in the MT *vs*. MTS group (Figure 5D); fatty acid biosynthesis, glycine, serine, threonine, pyrimidine, pantothenate and CoA biosynthesis, beta-alanine, arginine, proline, ascorbate, aldarate, D-glutamine and D-glutamate metabolism pathways were affected in the MT *vs*. NC group (Figure 5E); and pyrimidine, alanine, aspartate, glutamate, pantothenate and CoA biosynthesis, beta-alanine, citrate cycle (TCA cycle), butanoate, D-glutamine and D-glutamate, glycine, serine, and threonine metabolism pathways were affected in the MTS *vs*. NC group (Figure 5F). In general, these differentially altered metabolites were enriched in amino acid metabolism, lipid metabolism, glycometabolism, and nucleotide metabolism as shown in Figure 5G.

Screening of potential biomarkers

This study used 16 of the 156 differential metabolites to discriminate MT and MTS. The 16 metabolites were selected based on an increasing or decreasing trend from NC, MT to MTS, and significant differences in pairwise comparison to better distinguish the potential of MT patients to develop MTS (Figures 6A–P). Notably, acrylic acid, 3b-hydroxy-5-cholenoic acid, 5-amino-3-oxohexanoate, cytidine, D-ribose, L-glutamic acid, PE [P-18:1(9Z)/16:1(9Z)], PE [P-18:1(9Z)/20:3(5Z,8Z,11Z)], PE [P-18:1(11Z)/18:2(9Z,12Z)], PE [P-18:1(11Z)/18:3(6Z,9Z,12Z)], sorbitol, sphinganine, succinic acid semialdehyde, succinic acid, uracil, uridine, sphinganine, and succinic acid semialdehyde (MTS) had clear criteria for the progression of MT to MTS. Furthermore, receiver operating characteristic (ROC) curves were used to predict the class of subjects in the validation with a random forest (RF) model based on the data of the MT and MTS groups to evaluate the diagnostic potential of these metabolic biomarkers for MTS

TABLE 2 Correlations between metabolites and clinical variables.

Metabolite	Clinical Variable					
	Age		SOFA score		Glasgow score	
	r	*P* value	*r*	*P* value	*r*	*P* value
5-Amino-3-oxohexanoate	0.03742	0.7882	−0.2903	0.0315*	0.3252	0.0154*
PE [P-18:1(11Z)/18:2(9Z,12Z)]	−0.1111	0.4237	−0.07689	0.5769	0.2093	0.1251
PE [P-18:1(11Z)/18:3(6Z,9Z,12Z)]	−0.1174	0.398	−0.1494	0.2763	0.198	0.1473
PE [P-18:1(9Z)/16:1(9Z)]	−0.04119	0.7674	−0.1109	0.4203	0.337	0.0119*
PE [P-18:1(9Z)/20:3(5Z,8Z,11Z)]	−0.1571	0.2567	−0.1816	0.1844	0.185	0.1764
Sphinganine	0.08383	0.5467	0.2177	0.1103	−0.3101	0.0212*
3b-Hydroxy-5-cholenoic acid	−0.04752	0.7329	−0.3202	0.0172*	0.329	0.0142*
Acrylic acid	0.07945	0.568	0.2844	0.0353*	−0.09063	0.5105
Cytidine	−0.1624	0.2408	−0.3447	0.01*	0.2979	0.0272*
D-Ribose	0.1142	0.411	0.2382	0.0799	−0.1915	0.1612
L-Glutamic acid	0.22	0.1099	0.1458	0.2881	−0.1835	0.1799
Sorbitol	0.2203	0.1094	−0.1351	0.3255	0.01953	0.8875
Succinic acid	−0.2013	0.1444	−0.2231	0.1015	0.2217	0.1038
Succinic acid semialdehyde	−0.2483	0.0702	−0.3452	0.0099**	0.3682	0.0057**
Uracil	−0.08372	0.5473	−0.3425	0.0105*	0.3881	0.0034**
Uridine	−0.3173	0.0194*	−0.4536	0.0005**	0.396	0.0028**

The $P < 0.05$ were considered significant and marked with *, and $P < 0.01$ were marked with **. SOFA, sequential organ failure assessment.

patients. The area under the curves (AUC) of 5-amino-3-oxohexanoate, PE [P-18:1(9Z)/16:1(9Z)], sphinganine, cytidine, 3b-hydroxy-5-cholenoic acid, acrylic acid, D-ribose, sorbitol, succinic acid, succinic acid semialdehyde, uracil, and uridine are shown in Figures 6Q,R. Notably, the RF model based on the 12 biomarkers with significant differences showed good diagnostic performance in MTS patients.

Correlations between metabolites and clinical variables

This study used Spearman's correlation between the above 16 statistically significant metabolites and clinical variables (age, SOFA score, and Glasgow score) to determine the clinical availability of potential biomarkers further. The *P*-value and correlations (r) are shown in Table 2. The 5-amino-3-oxohexanoate, 3b-hydroxy-5-cholenoic acid, cytidine, succinic acid semialdehyde, uracil and uridine were negatively correlated with the SOFA score. In contrast, acrylic acid was positively correlated with the SOFA score. The 5-amino-3-oxohexanoate, PE [P-18:1(9Z)/16:1(9Z)], cytidine, 3b-hydroxy-5-cholenoic acid, succinic acid semialdehyde, uracil, and uridine were positively correlated with the Glasgow score, while sphinganine was negatively correlated with the Glasgow score. Moreover, uridine was negatively correlated with age. Therefore, the 9 noteworthy candidate biomarkers that are correlated with clinical variables may be suitable for the clinical diagnosis of MTS.

Identification of MTS biomarkers by UPHLC-MS/MS targeted quantitative analysis

To validate the 9 candidate metabolites (acrylic acid, 5-amino-3-oxohexanoate, 3b-hydroxy-5-cholenoic acid, cytidine, succinic acid semialdehyde, PE [P-18:1(9Z)/16:1(9Z)], sphinganine, uracil, and uridine) could accurately distinguish MTS from MT, another batch of 20 cases contains MT and MTS groups (10 cases in each group) was examined by UHPLC-MS/MS quantitative analysis. The results showed that succinic acid semialdehyde, uracil, and uridine had significant differences (Figure 7). Therefore, these results suggest that the three metabolites could be used as potential diagnostic biomarkers in MTS patients.

Discussion

Multiple trauma complicated with sepsis is one of the causes of high mortality in the ICU. Therefore, timely monitoring of sepsis progression in posttraumatic patients is crucial in MT treatment (26). Studies have shown that MT is the major risk factor for sepsis development. Moreover, early

sepsis diagnosis can prevent septic progression. However, the physiological mechanisms of sepsis are unknown. Furthermore, it is difficult to identify early biomarkers of sepsis. This study aimed to identify biomarkers of sepsis for early diagnosis using metabolomics analysis techniques. Metabolomics is a promising area of research because metabolome changes are more dynamic than the genome, and proteome changes quickly. Besides, metabolite changes can directly reflect the changes in many small molecules, such as nucleotides, amino acids, and lipids (27, 41). Although various studies have used metabolomics to screen biomarkers of trauma complicated with sepsis, these metabolites can only be used as diagnostic indicators and not for early diagnosis since these potential biomarkers are compared with normal people and MT patients (28, 42). Moreover, the identified diagnostic biomarkers were not specific for MTS. Although there are some advances in the metabolomics of sepsis, some factors still limit the clinical application of metabolomics. These biomarker candidates have failed validation in confirmation studies. Therefore, besides healthy controls, the design strategy of biomarker screening should also include controls with non-related diseases (29, 30, 32, 33). This study used plasma samples of healthy persons (NC), multiple trauma (MT), and multiple traumas complicated with sepsis (MTS) patients for metabolomics analysis. This study used UHPLC-MS for metabolomics detection. Previously, one-dimensional (1-D) proton (H) nuclear magnetic resonance (1H-NMR) was applied in metabolomics of sepsis, a recent study used 1H-NMR-based metabolomics to analyze and screen potential biomarkers for early diagnosis of metabolite concentrations between serum septic patients and healthy controls. The study showed that glucose, glycine, 3-hydroxybutyrate, creatinine and glycoprotein acetyl levels are higher in sepsis patients than in healthy controls. In contrast, citrate and histidine levels are lower in sepsis patients than in healthy controls (28). Although nuclear magnetic resonance (1H-NMR) and mass spectrometry (MS) combined with multivariate analysis can be used for sepsis metabolomics analysis, but MS has a greater sensitivity than NMR and presented a wider application prospect (31). Additionally, MS can accurately determine and quantify molecules and provide structural information of the detected compounds (43). Therefore, this study obtained several differential metabolites using UHPLC-MS technology, verifying its sensitivity and practicability.

Male sex, SOFA score and Glasgow score were the observably independent risk factors for the development of posttraumatic sepsis. A similar study showed that the age of patients and days of stay in the ICU are significantly different between sepsis ($n = 9$) and no sepsis ($n = 12$) groups (32). Furthermore, a study assessed 29,829 patients in Germany and showed that various factors, including male sex, preexisting medical condition, Glasgow Coma Scale score, Injury Severity Score, number of transfused red blood cell units, and number of operative procedures, are independent risk factors for the traumatic sepsis development. Additionally, the MTS patients have a longer stay in ICU, higher rates of organ failure and hospital mortality than the non-sepsis patients (33). Analogously, a systematic review involving 56,164 patients found that demographic factors, such as old age and male sex, are associated with an increased risk of sepsis (44). Herein, only age, SOFA score and Glasgow score were significantly different between the two groups, possibly due to the small sample size. Studies have reported that the incidence of sepsis is increased in elderly adults and age is an independent predictor of sepsis mortality (34). SOFA score has been widely used in septic evaluation, showing a moderate prognostic stratification ability (45). The Glasgow coma scale has been incorporated into the new sepsis recommendation (Sepsis 3.0). It can also be used to evaluate the mental state of patients with sepsis since sepsis can induce central nervous system infection and diffuse brain dysfunction (46). Therefore, these studies support our results of clinical characteristics to some extent.

Sepsis researches focus on exploring an ideal biomarker. Researchers have been exploring an ideal biomarker that can quickly and sensitively distinguish the presence and progression of sepsis. The early clinical diagnosis of sepsis depends on the presence of microbiologic cultures in blood. However, positive results are detected in only 30% of patients with sepsis or septic shock. As a result, studies have focused on the effects of metabolites produced by sepsis on individuals. Several biomarkers, such as procalcitonin, C-reactive protein, interleukin (IL)-6, and other inflammatory factors, have been proposed for sepsis detection (47). However, the clinical use of the existing biomarkers is limited. Although advances have been made in biomarkers for sepsis diagnosis, no single biomarker can meet the needs of specificity and sensitivity to distinguish sepsis from other inflammatory processes. Therefore, omics techniques, especially metabolomics, have been used to identify new biomarkers for sepsis progression. Although some studies use transcriptome or proteomics to screen sepsis biomarkers, metabolomics based on UHPLC-MS can also assess the effects of transcription and translation levels *in vivo*. Moreover, non-targeted metabolomics can systematically and comprehensively evaluate the unknown mechanism (35, 36). Therefore, metabolomics may play a critical role in the identification of sepsis biomarkers. Besides, the combined analysis of metabolomics and transcriptome or proteomics may be an important direction for the discovery of sepsis biomarkers in the future. Human serum, plasma and urine samples can be used to study the metabolome of sepsis to find promising biomarkers. Although various studies have used LC/MS techniques for sepsis metabolomics, the differential metabolites obtained in each study are different, possibly due to the resolution of the mass spectrometer used and the cause of sepsis.

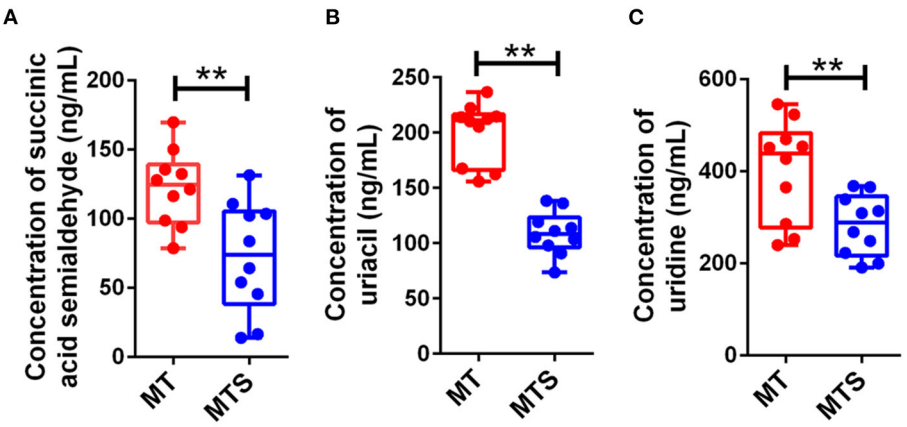

FIGURE 7
Candidate biomarkers were identified by UHPLC-MS/MS quantitative analysis in another batch of 20 cases ($n = 10$ in MT and MTS groups, respectively). **(A)** Succinic acid semialdehyde. **(B)** Uracil. **(C)** Uridine. $^{**}P < 0.01$.

Herein, 1,520 differential metabolites were detected between MT and MTS from the plasma of patients. The metabolites were enriched in amino acid metabolism, glycometabolism, lipid metabolism, nucleotide metabolism and other metabolic pathways. Some amino acids were lower in MTS patients than in the MT or NC groups, indicating that protein metabolism is a consumption process of amino acid in sepsis. The heterogeneity of the etiology of sepsis may lead to the different differential metabolites or potential biomarkers obtained *via* metabolomics in the early sepsis diagnosis. However, further studies are needed to assess the confirmation and regulatory mechanisms of these potential biomarkers in the clinical diagnosis of sepsis. The lower levels of glucose and organic acids, such as succinic acid, glutaric acid and pyruvic acid suggested that the citrate cycle (TCA cycle) and glycolysis/gluconeogenesis metabolism were disturbed in the MTS group. The intermediate products of the TCA cycle were significantly changed in the sepsis group than in the NC and MT groups, indicating that energy metabolism was disturbed in the sepsis group, thus decreasing energy production. An omic technologies review showed that sepsis affected the intermediate metabolite levels of the TCA cycle and is associated with mitochondrial beta-oxidation dysfunction of fatty acid metabolism (37). Furthermore, the inhibition of the TCA cycle requires energy supply through the anaerobic respiration pathway of glycolysis, leading to the conversion of pyruvate to alanine. The TCA cycle of mitochondria is the main pathway for the conversion of glutamine to CO_2 and pyruvate (38). Mannose levels were higher in the plasma of the MTS and MT groups than the mannose levels in the NC group, and the alteration was enriched in mannose metabolism (15). Moreover, numerous lipids and lipid-like molecules were significantly affected in the MTS group compared with the MT or NC group. These differential metabolites were enriched in metabolic pathways of glycerophospholipid, sphingolipid, alpha-linolenic acid, arachidonic acid, linoleic acid, fatty acid, and fatty acid biosynthesis. A similar study showed that glycerophospholipids and sphingolipids are altered in sepsis patients (39). Lipids are involved in the initiation and regression of septic inflammation (40). Herein, unsaturated fatty acids, such as linoleic acid, alpha-linolenic acid and arachidonic acid, were significantly affected in the MTS group compared with the MT and NC groups. The double bonds of polyunsaturated fatty acids are attacked by oxidative stress in lipids. Moreover, peroxides and aldehydes generate chain reactions involved in lipid peroxidation-related signaling pathways associated with deleterious consequences (48). Molecules with anti-inflammatory properties have been found in omega-3 fatty acids eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid (49). A study also showed that oxidative stress and lipid metabolism promote sepsis development (50). Furthermore, other pathways, including urea cycle metabolism, glutathione metabolism, and primary bile acid biosynthesis, were also affected in the MTS group. These pathways play important roles in sepsis (51, 52). Therefore, this study provides evidence for the relationship between glucose or lipid metabolism and sepsis. Herein, the age of patients was significantly correlated with uridine, possibly due to the decreased expression of uridine phosphorylases in the aged, destroying uridine homeostasis (53). Glasgow coma scale was used to evaluate coma status in patients with sepsis. The results showed the Glasgow score was significantly correlated with some metabolites, including some central nervous system-related metabolites. Cytidine, uracil, uridine and sphingosine are associated with sepsis (15, 54–56). In this study, the 9 candidate metabolites was finally examined to quantitative analysis and the results suggested

that succinic acid semialdehyde, uracil, and uridine could be used as potential diagnostic biomarkers in MTS patients. Although these published studies support the reliability of the metabonomic results, the usefulness and reprocibility of these novel biomarkers should be further confirmed depend on larger sample size in clinical.

In conclusion, this study identified three metabolic markers for MTS diagnosis after various analyses through untargeted plasma metabolomics. Meanwhile, these biomarkers may be used to screen MTS and assess the state of heterogeneous sepsis patients. However, this study has some limitations. (a) This study had a small sample size; However, the study randomly screened and enrolled eligible patients into the cohort to reduce errors. (b) This study did not confirm whether these metabolic variates are related to the early sepsis stage. (c) The biomarkers were not specific to all sepsis patients due to the genetic polymorphisms and host differences. Therefore, larger cohort study studies are needed to verify the results and improve the understanding of the pathophysiology of trauma-induced sepsis, providing a basis for managing traumatized patients in the ICU, including early diagnosis, targeted therapy and follow-up investigation.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the General Hospital of Ningxia Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KF, WD, LL, SL, YG, and ZC performed the experimental research and data analysis. XF wrote and edited the manuscript. GC and XF contributed to the study design, data analysis, and writing and editing of the manuscript. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.923170/full#supplementary-material

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Modeling approaches for early warning and monitoring of pandemic situations as well as decision support

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The COVID-19 pandemic has highlighted the lack of preparedness of many healthcare systems against pandemic situations. In response, many population-level computational modeling approaches have been proposed for predicting outbreaks, spatiotemporally forecasting disease spread, and assessing as well as predicting the effectiveness of (non-) pharmaceutical interventions. However, in several countries, these modeling efforts have only limited impact on governmental decision-making so far. In light of this situation, the review aims to provide a critical review of existing modeling approaches and to discuss the potential for future developments.

KEYWORDS

pandemic, machine learning, artificial intelligence, agent-based-modeling, compartmental models

Introduction

In December 2019, a new virus (SARS-CoV-2), causing a respiratory disease - later named COVID-19[1], was discovered. At the time of the outbreak, many healthcare systems around the world were not well prepared for the pandemic that later emerged. While the virus was initially detected in China, measures to prevent its spread to other regions of the world were often hesitant and taken too late. Whereas compartmental spatio-temporal models of disease spread in epidemiology have been known in principle for a long time (1), many countries initially lacked robust and systematically collected surveillance data to which these models could be fitted. In general, it has been difficult to translate insights from modeling into actionable decision support for the government.

Based on these considerations, the French-German collaborative project AIOLOS (Artificial Intelligence Tools for Outbreak Detection and Response) has recently started

1 https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229

with the aim to strengthen the resilience of national healthcare systems against future outbreaks of respiratory infections[2]. More specifically, AIOLOS identifies three areas, where population-level computational modeling, including techniques from Artificial Intelligence (AI) and machine learning (ML), could potentially impact the preparedness against future pandemics based on various data sources (Figure 1):

1. early warning of a new outbreak,
2. monitoring the spatio-temporal spread of a disease,
3. predicting the impact and effectiveness of different interventions to support decision-making at scientific and policy levels.

This paper aims to review existing population-level computational modeling work in each of these areas. Our ambition is thus significantly different from published reviews, which solely focused on mathematical models of COVID-19 disease spread (2) or AI/ML algorithms for patient-level disease diagnosis and prognosis (3).

Early warning

Surveillance data

Health surveillance data is the traditional source of information for detecting a pandemic outbreak. The goal of respective computational approaches is to detect anomalies in a data stream consisting of discrete events, i.e., cases reported by doctors. For this purpose, several statistical tests have been suggested in the literature, including methods proposed by the Robert Koch Institute in Germany (4) and the Center for Diseases Control and Prevention in the USA (5), the Farrington method and its variants (6, 7) and Bayesian methods (4). Altogether, the R-package "surveillance" lists almost 20 algorithms for the early detection of pandemic outbreaks using surveillance data (8), covering three different scenarios:

1. spatio-temporal data of individual infectious events,
2. temporal event history of a defined set of individual units (e.g., specified households),
3. events aggregated over regions and time periods.

Due to data privacy concerns, typically only data of the last category are made publicly available and considered for governmental decision-making. A comparative simulation study pointed out elevated false positive rates for many algorithms with sensitivities ranging between 20 and 67% (9). Furthermore, a principal challenge is that traditional surveillance data in many countries are not systematically recorded in a fully automated and digitalized manner. Moreover, surveillance data in several countries do not cover several relevant aspects, such as hospitalization and ICU admission rates. Hence, this data could come too late for an early warning system. In response to this situation, several authors have thus proposed to systematically monitor wastewater for virus particles rather than waiting for reports by doctors (10, 11), and according measures are currently being implemented in the USA, Europe, and Israel. Noteworthy, Israeli researchers already used such an approach a few years ago to detect a silent polio outbreak (12, 13).

Social media

Given the shortcomings of traditional surveillance data, several authors have more recently explored the potential of social media. Jain and Kumar (14) proposed a keyword extraction approach, in which they first used the term frequency-inverse document frequency (TF-IDF) technique, identifying relevant keywords from tweets, and secondly, used a linear discriminant analysis (LDA)-based classifier to find relevant keywords in newspaper really simple syndication (RSS) feeds. Subsequently, the relevant keywords were used to analyze tweets from the respective period, and machine learning classifiers were developed to filter out irrelevant tweets. They found that Support Vector Machines (SVMs) and a Naive Bayes classifier most accurately classified tweets ($F_1 = 0.77$).

Lopreite et al. (15) performed statistical tests (Kolmogorov-Smirnov and Anderson-Darling) to compare the cumulative frequencies of pneumonia-related tweets from the winter seasons of 2018/2019 and 2019/2020 in selected European countries. They found an exceeding number of pneumonia-related postings in the winter season of 2019/2020 before the outbreak of COVID-19. In a similar direction, Mavragani (16) retrieved Google Trends data for the topic of "Coronavirus" and calculated Pearson correlation coefficients between Google Trends data and the respective categories of cumulative/daily cases/deaths. The results showed strong correlations of Google Trends data with COVID-19 cases and deaths in the examined European countries. The authors conclude that *information epidemiology* is a viable instrument to monitor the disease spread and identify regions in which cases have not yet peaked, hence contributing to an early warning system.

Going methodologically one step further, Yousefinaghani et al. (17) used a real-time anomaly detection approach utilizing the Seasonal-Hybrid Extreme Studentized Deviate algorithm (18) to identify the onset and peak of COVID-19 waves in Google Trends and Twitter data from the US and Canada. This study also evaluated the correlation between tweets and Google trends data with official COVID-19 case numbers. Pearson correlation analysis demonstrated a strong correlation between officially reported infected cases and the relevant posts

2 https://www.digitale-technologien.de/DT/Redaktion/EN/Standardartikel/Internationale_Koop_Projekte/Frankreich/ki_innovationsprojekte_de_fr_projekt_aiolos.html

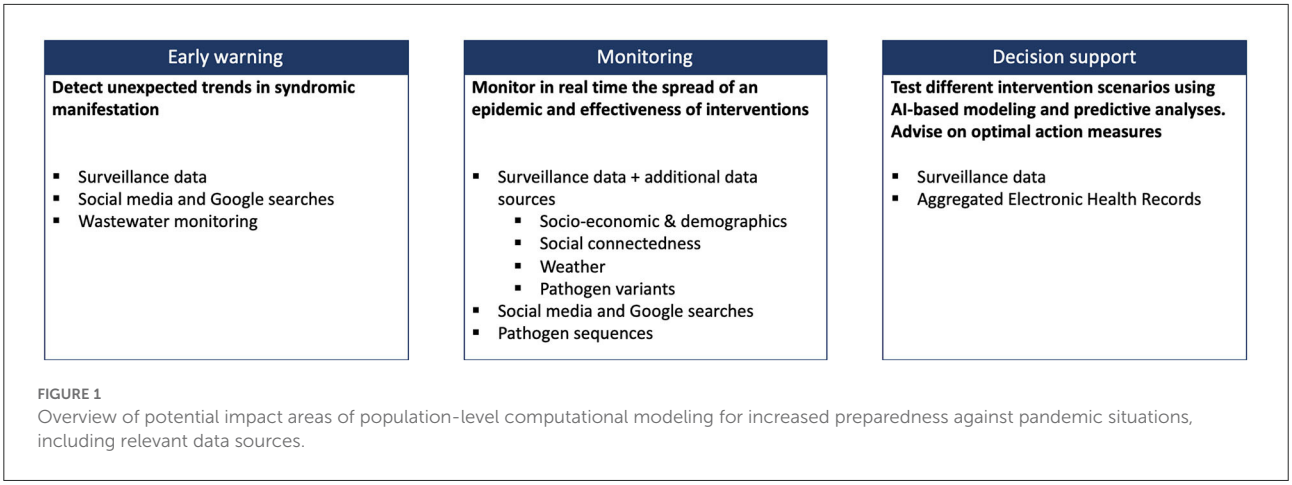

FIGURE 1
Overview of potential impact areas of population-level computational modeling for increased preparedness against pandemic situations, including relevant data sources.

TABLE 1 Included early warning studies.

Studies	Data source	Technique(s)
Höhle (4), Stroup et al. (5), Farrington et al. (6), Noufaily et al. (7), Meyer et al. (8), Lastra et al. (10), Maida et al. (11), Sharara et al. (12), Brouwer et al. (13)	Surveillance Data (health data, wastewater)	R package "surveillance," anomaly detection, statistical tests
Jain and Kumar (14), Mavragani (16), Yousefinaghani et al. (17), Hochenbaum et al. (18), Broniatowski et al. (19), Kogan et al. (20)	Social Media (Twitter, Google trends, Newspaper feeds, UpToDate)	Keyword extraction, TF-IDF, anomaly detection, classifier (SVM, Naive Bayes), statistical tests (Kolmogorov-Sminrvov, Anderson-Darling, Pearson correlations), BM

TF-IDF, term frequency–inverse document frequency; SVM, Support Vector Machine; BM, Bayesian Model.

and searches. Unlike other studies, the authors quantitatively prioritized COVID-19 symptoms in detecting disease trends. For example, "cough" and "fever" were better trend indicators compared to "tiredness" and "loss of smell."

Broniatowski et al. (19) identified health-related, influenza-related, and case-reporting tweets with logistic regression, which were used with Google Flu Trends to predict influenza outbreaks at municipal and regional levels.

Further, Kogan et al. (20) used a Bayesian probabilistic model to develop an early warning algorithm for COVID-19 based on social media (Google Trends, Twitter, UpToDate), fever incidence rates, and predictions made by the global epidemic and mobility model (21), resulting in a time-to-event prediction. The algorithm was validated on COVID-19 surveillance data as well as incidence rates of influenza-like illness, demonstrating that an uptrend in COVID-19 infections could be predicted up to 7 days in advance with an accuracy of ∼75%. Table 1 summarizes the techniques employed by the discussed papers.

Disease monitoring

Spatio-temporal modeling of disease spread

There are different approaches for modeling the spatio-temporal spread of an epidemic situation described in the literature (see Tables 2–5):

- mechanistic compartmental models formulated as differential equation systems, which have been classically used in epidemiology (22, 26–33, 35–38, 40, 64),
- machine learning approaches, including Bayesian learning techniques (41–49),
- agent-based modeling approaches (50–55),
- hybrid modeling approaches combining several of the aforementioned techniques (39, 56, 58–63, 65).

Compartmental models

General principle

To model and understand the evolution of an epidemic, compartmental models are often used. The underlying idea is to distribute the population into several interconnected compartments. The relationship between these compartments is given by a system of differential equations. With given or estimated initial conditions this mathematical system can be solved at any point in time The foundation of today's

TABLE 2 Included studies covering spatio-temporal monitoring of disease spread with compartmental models and their key aspects.

Study	Key aspects
Zhang (22)	Include factor for incubation time, immunity, and control efforts
Shaman et al. (23)	Use an EAKF to adjust (un)observable state variables
Leonenko and Ivanov (24)	Model dynamics of influenza outbreaks on city level
Osthus et al. (25)	Relate SEIR to state-space model and expand parameter vector
Aravindakshan et al. (26)	Estimate connection between NPIs and social mobility: used in the model
Bahri (27)	Splits between young and older population and estimates efficacy of NPIs
Bertozzi et al. (28)	Compare three basic models for different stages of pandemic
Chang et al. (29)	Introduce mobility networks between CBGs and POIs
Coudeville et al. (30)	Estimate effect of NPIs on industry decisions
Giordano et al. (31)	Model distinguishes between detected and undetected and among SOI
Götz and Heidrich (32)	Use registered deaths as parameter including a delay-term
Khan et al. (33)	Include detected and undetected cases and measure the effect of NPIs
Pei et al. (34)	Investigate spatial dynamic coupling across locations for asynchronous NPIs
Prague et al. (35)	Augment data to account for random effects and to increase accuracy
Coudeville et al. (36)	Study vaccination with different immunization programs
Humphrey et al. (37)	Introduce isolation compartment to study social distancing
Kheder et al. (38)	Introduce multiple discrete stages to account for multiple waves
Sartorius et al. (39)	Study different spatial patterns (e.g., of mortality) in small areas
Schüler et al. (40)	Implement effect of NPIs by using a piecewise constant transmission rate

EAKF, ensemble adjustment Kalman filter; SEIR, susceptible-exposed-infected-recovered; NPI, non-pharmaceutical intervention; CBGs, census block groups; POIs, points of interest; SOI, severity of illness.

TABLE 3 Included studies covering spatio-temporal monitoring of disease spread with machine learning and Bayesian models and their key aspects.

Study	Key aspects
Stojanović et al. (41)	Introduced a spatio-temporal kernel function
Al-qaness et al. (42)	Forecast for the upcoming days with a fair amount of data
Fong et al. (43)	Develop forecasting model with insufficient amount of available data
Mehta et al. (44)	Estimate outbreak probability on county level
Pavlyshenko et al. (45)	Investigated impact on stock market
Suzuki et al. (46)	Use binary classification to see if number of cases will exceed a threshold
Ibrahim et al. (47)	Implement urban characteristics and index for NPIs
Nader et al. (48)	Estimate growth rate depending on specific NPI
Yeung et al. (49)	Compared non-time series ML algorithms to model pandemic

NPI, Non-Pharmaceutical Intervention; ML, machine learning.

TABLE 4 Included studies covering spatio-temporal monitoring of disease spread with agent-based modeling approaches and their key aspects.

Study	Key aspects
Hoertel et al. (50)	Estimate impact of post-lockdown measures and introduce shielding of PAR
Hinch et al. (51)	Estimate effect of contact tracing with mobile app
Keer et al. (52)	Model by calculating probability of agent to change state at a timepoint
Staffini et al. (53)	Retrospectively study effect NPIs had and additional NPIs could have had
Colosi et al. (54)	Estimate reproduction numbers for different VOC in schools
Shattock et al. (55)	Analyze different NPI and vaccination strategies

PAR, persons at risk; NPI, non-pharmaceutical intervention; VOC, variance of concern.

compartmental models was formulated nearly a century ago (1). In their study, Kermack and McKendrick examined the evolution of various pandemics and established the commonly used susceptible-infected-removed (SIR) model which is based on three compartments:

- $S(t)$ - The **susceptible** population, i.e., the part of the population that can become infected,
- $I(t)$ - The **infected** population, i.e., the part of the population that has the disease and can transmit the disease to the susceptibles,
- $R(t)$ - The **removed** or **recovered** population, i.e., the part of the population that has recovered from the disease and that is considered immune.

(With $N = S(t) + I(t) + R(t)$ being the total population.)

TABLE 5 Included studies covering spatio-temporal monitoring of disease spread with hybrid models and their key aspects.

Study	Key aspects
Dandekar and Barbastathis (56)	Analyze NPIs in different countries to find effective reproduction number
Menda et al. (57)	Estimate dynamic transmission number with NN, allowing for multi-peaks
Silva et al. (58)	Build society with ABM and simulate different NPI scenarios
Capobianco et al. (59)	Combine ABM and SEIR with Markov model and RL for NPI planning
Wang et al. (60)	Combine spatial and temporal models
Watson et al. (61)	Predict deaths by relation between cases and population characteristics
Fritz et al. (62)	Use a GNN to include local mobility and connectedness data from Meta
Hadley et al. (63)	Modify transmission and hospitalization rates fitted to agent's characteristics

NPI, non-pharmaceutical intervention; NN, neural network; ABM, agent-based modeling; SEIR, susceptible-exposed-infected-recovered; RL, reinforcement learning; GNN, graph neural network.

The dynamics of the SIR model get described by a set of ordinary differential equations (ODEs), which include two free parameters, β - the transmission rate and γ - the recovery rate:

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I.\end{aligned}$$

Due to its simple nature, there are also some limitations and assumptions with this model. Here we will mention some of them. First, the population size is assumed to be constant, the birth nor the death rates are incorporated, and the model does not allow for people to become reinfected. Second, both the transmission and the recovery rates are constant. Third, the model assumes that the infected person becomes infectious immediately after getting infected, whereas in reality there is a latency period. Another assumption is that there is homogeneous mixing of the population, and no social networks and mobility are considered.

To account for some of its limitations, the archetypical SIR model can be extended to include an age structure or additional compartments, e.g., compartment E for the - by the virus-exposed - population (susceptible-exposed-infected-removed: SEIR), compartment D for the disease-deceased population or compartment H for the hospitalized population.

Applications to epidemic disease monitoring

There is a vast literature on compartmental disease models over the last 50 years (66). Examples include the successful modeling of several epidemic outbreaks, such as SARS (22) and influenza (23–25). However, the highly dynamic development of the COVID-19 pandemic with corresponding public intervention measures required extensions and modifications (26, 27, 30, 32, 36, 37, 40). For example, Götz and Heidrich (32) used the number of registered deaths by COVID-19 rather than the registered cases, with the idea to evade the dark figure of undetected cases, including a delay term to account for the time between infection and death. Bahri (27) split between a young population (age $<$60 years) and an older population (age $\geq$60 years) stating that the younger population has more infections, while the older population is at higher risk, with a much higher death rate. Similarly, Coudeville et al. (30) introduced an age-stratified SEIR model to estimate how different scenarios affect industry decisions on different time scales. In another study, the authors further used this model to derive the potential effects of various immunization programs based on vaccination (36).

Aravindakshan et al. (26) used a compartmental model including social distancing and mobility as parameters. The authors further estimated the impact of different non-pharmaceutical interventions (NPIs) on social distancing including other covariates (e.g., weather, day of the week) in a linear regression model and used its coefficients for simulating different scenarios. Schüler et al. (40) included NPIs by using a piecewise constant transmission rate depending on the corresponding NPI and analyzed effects on the district level. Similarly, Humphrey et al. (37) estimated the effect of testing and tracing in combination with social distancing measures by introducing an isolation compartment, resulting in a modified transmission rate. Prague et al. (35) estimated several parameters of an extended SEIR model from data about the incident and hospitalized cases in France at a regional level *via* a non-linear mixed effects model while considering NPIs. Moreover, the model by Prague et al. considers the fact that only a fraction of the actually infected patients is counted in surveillance data.

Bertozzi et al. (28) studied the disease spread in several European countries, first looking at the exponential growth and the self-exciting branching process and then using a compartmental model, focusing on the impacts of social distancing, enabling them to model and understand different stages of the pandemic.

Khan et al. (33) modeled an NPI-dependent transmission rate. Chang et al. (29) modeled the disease spread in the ten largest US metropolitan areas using bipartite networks with time-varying edges for mapping the hourly movement of census block groups (CBGs) to specific points of interest (POIs). Then, each mobility network gets paired with an extended SEIR model with a corresponding transmission rate. To illustrate the spatial dynamic coupling across locations, Pei et al. (34) used a metapopulation SEIR model including daily work commuting

and random movement among 3,142 US counties. Using inference, they studied the effect of asynchronous interventions across these locations in the US and performed counterfactual simulations to estimate the evolution of the disease spread by implementing NPIs at different times. To account for the fact that COVID-19 is a pandemic with several waves, Khedher et al. (38) introduced multiple discrete states into their model.

Sartorius et al. (39) developed a discrete-time SEIR model, which incorporated information about population density and mobility using a hierarchical Bayesian model. They estimated their model *via* full Bayesian inference (Markov Chain Monte Carlo sampling).

Machine learning models

In addition to compartmental models, machine learning techniques, including neural networks, have become popular approaches for modeling and predicting disease spread. Examples include models for the disease spread in China (43) and worldwide (47). Fong et al. (43) tried to overcome the problem of a small dataset by using a *polynomial* neural network with corrective feedback, while Ibrahim et al. incorporated urban characteristics and NPIs *via* a variational Long Short-Term Memory (LSTM) encoder.

In addition to neural networks, other machine learning techniques have been proposed as well: for example, Al-qaness et al. (42) combined an Adaptive Neuro-Fuzzy Inference System (ANFIS) with a flower pollination algorithm (FPA) using the salp swarm algorithm (SSA), creating the FPASSA-ANFIS model. Nader et al. (48) developed a Random Forest algorithm; other studies employed extreme stochastic gradient boosting (XGBoost) (44, 46). Yeung et al. (49) compared different classical machine learning regression methods (ridge, decision tree, Random Forests, AdaBoost, and Support Vector Machines) and found Random Forests and AdaBoost to perform best. In general, classical, non-time series machine learning models could predict future pandemic development rather accurately.

Pavlyshenko (45) used a Bayesian machine learning approach for modeling the global spread of COVID-19 and its effect on the stock market, while (41) additionally included the spatial aspect *via* a spatio-temporal kernel function.

Agent based models

Agent-based modeling (ABM) is a sub-field of Artificial Intelligence (AI). The idea in ABM is to simulate a set of software agents, which can interact with each other according to a defined set of rules. ABM approaches can implement many characteristics such as social contacts of individuals or sub-populations, disease characteristics (e.g., virus transmission rates, virus variants), patient characteristics (e.g., age, sex, comorbidities, and risk factors), mobility and contact networks (e.g., household, workplace, school, community, tourism), healthcare services (e.g., hospitalization, bed occupancy) and governmental regulations or NPIs.

In the literature, ABM approaches have been used on different scales. Staffini et al. (53) used socio-economic and disease-related information to study the spread of the SARS-CoV-2 virus and the influence of NPIs in Italy, Germany, Sweden, and Brazil. Shattock et al. (55) included risk groups and seasonal patterns in the transmission model and estimated the effect of various NPIs as well as vaccination campaigns on the pandemic evolution, hospitalization, and deaths in Switzerland. Colosi et al. (54) used an ABM approach to estimate school-specific reproduction numbers depending on the COVID-19 variants.

Various authors further extended these models by including demographic features as well as more profound contact networks - through deeper population mobility simulations - to simulate synthetic populations, the disease spread in this population, and the effect of a large set of NPIs (50–52). Hoertel et al. (50) focused on possible post-lockdown measures to reduce epidemic rebounds and therewith estimated the effect of protecting/shielding persons at risk; while Hinch et al. (51) and Kerr et al. (52) both developed a simulation platform, *OpenABM*, and *Covasim*, which enables to simulate the disease spread depending on various settings, including different NPIs.

Hybrid models

One of the main limitations of machine learning is the assumption of test data being drawn from the same statistical distribution as training data. This results in a major challenge if there is a covariate shift of test data relative to the original training data, e.g., due to NPIs, seasonal effects, new virus variants, or further unknown factors. Hence, the utility of conventional machine learning models in a highly dynamic situation such as the COVID-19 pandemic must be questioned. In this regard hybrid modeling approaches combining compartmental models and machine learning, or compartmental models and ABM approaches could provide an interesting alternative.

Several authors have explored hybrid models of the spatio-temporal disease spread in this regard: For example, Dandekar and Barbastathis (56) used a neural network to model the influence of NPIs on the compartment of infected patients. For model training, they employed the universal ODE approach, which combines neural networks with ODEs in a joint framework (67). Menda et al. (65) introduced a neural network to relax the assumption of a constant transmission rate. Their model is formulated as a non-Gaussian state-space system, which is estimated *via* Certainty-Equivalent Expectation-Maximization (57).

Wang et al. (60) combined their extended SIR model with spatial cellular automata (CA) and then introduced a Convolution Neural Network (CNN) paired with an LSTM

recurrent neural network to learn the dynamical parameters of a compartmental model, which also includes the population of undetected or asymptomatic individuals.

Watson et al. (61) first used a probabilistic graphical model estimated *via* Bayesian inference to predict the velocity of cumulative cases. Moreover, they developed a Random Forest model to give daily projections and interval estimates for cases and deaths in different US states. Both models were then combined into a compartmental model to make forecasts of incidence rates.

A different type of hybrid model is presented by Fritz et al. (62). They combined a statistical spatial regression with a Graph Neural Network (GNN) incorporating social connectedness and co-location maps.

Several authors combined ABM approaches with SEIR models (58, 59, 63). Hadley et al. (63) derived the transmission and hospitalization rates depending on the agent's age, comorbidity status, and testing status to forecast the ICU bed demand. Silva et al. simulated a society (i.e., persons, houses, businesses, government, and healthcare systems) including a large set of social and demographic parameters and estimated different scenarios based on social distancing measures. Capobianco et al. introduced the *PandemicSimulator* including – besides a SEIR model – a moving and interacting society, a government that makes policy decisions, and optional testing and contract tracing strategies. They also suggested adding a hidden Markov model to adapt infection rates over time and a reinforcement learning (RL) layer to find the optimal policy to minimize the public health impact.

Social media and internet searches

The epidemic spread has been shown to be correlated with search engine usage on the web in the past (68). Nowadays people also share their opinion on social media networking sites such as Twitter, Reddit, and Facebook. These opinions can also be utilized to track epidemic disease spread. Masri et al. (69) studied using tweets' time and geolocation data to improve the monitoring of the Zika virus (ZIKV) epidemic. The collected tweets were counted and compared with weekly data of the U.S. ZIKV cases, revealing a high Pearson correlation coefficient value of 0.67 by applying a 1-week lag on tweets. Adding this 1-week-lag tweet data to the case counts in an auto-regression prediction model improved the coefficient of determination (R^2) from 0.61 to 0.74, which showed that tweet metadata is a significant predictor of future ZIKV cases.

Various authors have also used social media to support the surveillance and monitoring of an epidemic (70–72). Missier et al. (70) identified tweets related to dengue epidemics by classifying them into mosquito, sickness, and news-related classes. Chen et al. (73) created an ongoing collection of so far 123 million COVID-19-related tweets identified using various keywords and shared it with the research community for further analysis.

To better understand and model the trajectory of COVID-19 in the US, Klein et al. (74) manually annotated 10,000 pre-filtered tweets into three COVID-19 associated classes (probable, possible, and other cases) and used Bidirectional Encoder Representations from Transformers (BERT) to automatically classify tweets. The classifier achieved an F_1 score of 0.64 for differentiating three classes. Given that "probable" or "possible" tweets were primarily distributed in the states reporting COVID-19 cases and posted before the first confirmed case, the model could successfully identify candidate COVID-19 cases and high-risk regions.

Similarly, Liu et al. (75) collected COVID-19-related Reddit posts from North Carolina, which showed a similar trend of observed confirmed cases and deaths as to the government data. They further classified these posts while performing NER to obtain mitigation types (such as distancing, disinfection, personal protective equipment) and detection types (such as symptoms, testing) and analyzed for a certain time period the change of people's sentiments toward masks in these posts. For disease monitoring, Magge et al. (76) built a system to collect symptoms and disease mentions from social media platforms and normalized them to unified medical language system (UMLS) terminology. Using deep learning methods (such as BERT and RoBERTa) that were trained on multiple available corpora (such as TwiMed, MedNorm, DS-NER), they achieved an F_1-score of 0.86 and 0.75 on DailyStrength and Twitter datasets, respectively. They also applied their system on Twitter posts to collect COVID-19 symptoms.

Users also share their opinions on COVID-19 measures on Twitter by supporting, refuting, or just commenting on them (77). These opinions from German-speaking countries were manually labeled, and Beck et al. utilized predictions by transformer-based models. Jalil et al. (71) performed sentiment analysis on tweets' text to classify them into positive, negative, and neutral. For the analysis, they used the *COVIDSenti* dataset (78) and reached the highest accuracy of 96.66% with the proposed Multi-depth DistilBERT method. Table 6 provides an overview of the use of social media and internet searches for disease monitoring.

Pathogen sequences

Pathogens are, like any organism, under evolutionary pressure and will thus mutate to optimize their adaptation to the human host. Accordingly, different pathogenic variants will occur over time. Deep learning approaches have recently been introduced to identify such variants during sequencing (79). In addition, phylogenetic tree inference, a classical approach from computational biology based on a sequence alignment followed by a statistical tree inference (either maximum

TABLE 6 Included studies focusing on disease monitoring *via* mining of social media and internet searches.

Study	Aim	Technique(s)
Ginsberg et al. (68)	Analyzed search queries to monitor influenza-like illness	Linear model
Missier et al. (70)	Compared methods for detecting disease related tweets	SC and LDA
Jahanbin et al. (72)	Developed text-mining method for disease related tweets	FAEMC-ID
Masri et al. (69)	Used tweets to predict future ZIKV cases	Auto-reg. prediction
Chen et al. (73)	Collected COVID-19 related tweets	Keyword collection
Klein et al. (74)	Modeled the COVID-19 disease spread with associated tweets	BERT
Beck et al. (77)	Analyzed tweets about reaction to COVID-19 measures	Ger-BERT
Liu et al. (75)	Analyzed tweets for cases and deaths and people's sentiments	NER
Magge et al. (76)	Monitored COVID-19 disease spread and collected symptoms	BERT and RoBERTa
Jalil et al. (71)	Analyzed tweets for people's sentiments and classified them	DistilBERT

ZIKV, Zika-virus; SC, supervised classification; LDA, linear discriminant analysis; FAEMC-ID, fuzzy algorithm for extraction; monitoring; and classification of infectious diseases; Auto-reg., auto-regression; BERT, bidirectional encoder representations from transformers; Ger-BERT, German bidirectional encoder representations from transformers; NER, named entity recognition; RoBERTa, robustly optimized bidirectional encoder representations from transformers approach; DistilBERT, distilled bidirectional encoder representations from transformers.

likelihood or Markov Chain Monte Carlo) with a dedicated likelihood function (80), is often used. Incorporation of spatio-temporal information into the construction of phylogenies could potentially provide important information on the spread of virus variants. Still, phylogenies are not only informed by pathogen sequences, but also by external factors, such as the sampling process, the proportion of the pathogen genome sequenced in each sample, the quality of the sequence data, and the mutation rate of the pathogen itself (81).

Several authors have suggested approaches to construct temporal phylogenies (82–84) and applied this strategy to SARS-CoV-2 (85–87). More recently, Didelot et al. (88) showed that transmission events between hosts could be estimated by coloring different hosts in a phylogenetic tree reconstruction. Müller et al. (89) extended phylogenies to networks by incorporating recombination events and applied this strategy to influenza.

New variants may influence the transmission rate of a pathogen. Davies et al. (90) first retrospectively estimated the lineage-dependent growth rates of SARS-CoV-2. Based on that, they further calculated the expected competitive advantage of a new lineage and predicted the impact on the reproduction and the transmission rates *via* a discrete-time compartmental spatio-temporal disease model.

Decision support

Healthcare resource planning

Modeling can not only help to alert and monitor a pandemic situation, but forecasts generated by corresponding models can also give guidance on necessary actions. Therefore, there is no clear boundary between early warning, monitoring, and decision support.

One important aspect of decision support is the management and planning of available public healthcare resources. In this regard, Ivorra et al. (91) developed a compartmental model for China, in which they included the hospitalization rate. With the help of their model, they estimated and planned the demand for clinical beds. With a similar ambition in mind, Hadley et al. (63) proposed an agent-based modeling approach. Lorenzen et al. (92) developed a machine learning model (Random Forest) using electronic health records of more than 40,000 patients in Denmark, which predicted the number of ICU admissions and ventilator use. Kandula et al. (93) developed a compartmental model for predicting influenza hospitalization rates using Google search trends. Moa et al. (94) proposed a linear model to forecast the overall severity of an influenza season in Australia based on only five parameters.

Planning and evaluating NPIs

In addition to healthcare resource planning a further aspect of modeling is to support the planning and evaluation of NPIs. In this context three different types of studies have been conducted (see Table 7):

- those that retrospectively evaluate the effects of NPIs (26, 27, 31–34, 40, 48, 49, 56, 60, 97, 98),
- those that make forecasts on the effects of a specified NPI in the sense of scenario planning (26, 31, 35, 38, 50–55, 58, 96),
- and those that develop methods for optimal control policy identification (59, 100–104).

TABLE 7 Included studies covering decision support.

Studies	Technique(s)
Healthcare resource planning	
Ivorra (91), Kandula et al. (93)	CM: including or predicting hospitalization rates
Moa et al. (94)	Linear model
Hadley et al. (63)	Agent-based modeling
Lorenzen et al. (92)	Random Forest using electronic health records
NPI evaluation	
Schüler et al. (40), Aravindakshan et al. (26), Khedher et al. (38), Giordano et al. (31), Prague et al. (35), Dandekar and Barbastathis (56)	CM: introducing NPI effect on transmission rate and reproduction number
Mader and Rüttenauer (95)	SCT: analyze effect of vaccinations
NPI scenario planning and forecasts	
Khedher et al. (38), Giordano et al. (31), Prague et al. (35), Kissler et al. (96)	CM
Staffini et al. (53), Shattock et al. (55), Colosi et al. (54), Hoertel et al. (50), Hinch et al. (51), Kerr et al. (52), Silva et al. (58)	ABM and hybrid ABM
Flaxman et al. (97)	Bayesian hierarchical model
Yeung et al. (49), Nader et al. (48), Barros et al. (98), Haug et al. (99)	ML
NPI development	
Kwak et al. (100), Colas et al. (101), Khadilkar et al. (102), Padmanabhan et al. (103), Chadi and Mousannif (104)	CM and RL: including health and economic costs
Capobianco et al. (59)	Hybrid ABM and RL

CM, compartmental models; NPI, non-pharmaceutical intervention; SCT, synthetic control technique; ABM, agent-based modeling; ML, machine learning; RL, reinforcement learning.

Retrospective evaluation of NPIs is generally challenged by the fact that NPIs are highly heterogeneous. Historically, often several NPIs have been applied at the same time, and there is neither a control group nor any kind of randomization. Systematic differences across countries in terms of demography, population density, climate, or cultural aspects complicates using of one country as a control for another one, even if typical statistical matching or weighting techniques known from observational studies are applied. Moreover, there is the question of the corresponding outcome to consider, given that observed incident cases will depend on the applied test strategy and thus underestimate the true number of infected people.

One type of approach has been to try to associate NPIs with the spatio-temporal modeling of disease spread, e.g., by introducing the NPI effect on the transmission rate and reproduction number in a compartmental model (26, 31, 35, 38, 40, 56). Correspondingly, authors have then used such models to make scenario forecasts, e.g., regarding the effect of social distancing (31, 35, 38, 96). Also, other types of spatio-temporal disease spreading models have been used for the same purpose, such as ABM approaches (50–55, 58), Bayesian hierarchical modeling (97), and machine learning (48, 49, 98, 99). The work of Yeung et al. specifically investigated the influence of socio-cultural aspects on the growth rate of COVID-19 incidences in 114 countries. The work by Barros et al. considered causal machine learning techniques.

Also, more traditional statistical analysis approaches have been applied recently, such as the synthetic control technique (95), which uses incident case numbers from the same country in the treatment and control group, depending on when an NPI has been put in place. Additionally, Mader and Rüttenauer analyzed the effect of vaccinations.

To find optimal control policies, offline RL strategies have been proposed by several authors. While Kwak et al. (100) solely relied on deep learning and only focused on health aspects, other studies (101–104) focused on a hybrid modeling strategy incorporating an extended SEIR compartmental model for predicting potential NPI effects. Moreover, the latter studies incorporated the economic costs of NPIs as well. Finally, Capobianco et al. (59) combined their hybrid ABM approach with offline RL to optimize the reopening policies.

Discussion

Statistical tests have been used traditionally to detect outbreaks based on surveillance data. Recent years have witnessed an increasing use of other data sources, such as social media and internet searches. Even though such data types are likely to contain relevant signals, these are most likely biased toward certain user communities. Hence, early warning signals detected *via* "digital traces" should be seen as a complement to traditional surveillance data, but not as a replacement.

Regarding the monitoring of pandemics, specifically, the existing modeling efforts for COVID-19 have highlighted numerous challenges, such as the unknown number of truly infected persons (due to limitations of tests and test strategies, or due to asymptomatic disease) and the dependency on the spatio-temporal spread on external factors, such as NPIs and the compliance to those measures, weather, population density, and socio-economic aspects. Hence, many authors have extended traditional epidemiological compartment models and combined them with statistical inference and machine learning techniques, partially resulting in hybrid neural network /compartmental modeling approaches. While these are clear advancements, it

should be seen that the spatio-temporal spread of an infectious disease is generally determined by a complex interplay between a pathogen (e.g., its genetic adaptability), individual (e.g., genetic variants, disease history, lifestyle, socio-economic conditions), society (e.g., testing strategy, vaccination rate, NPIs and compliance to those, population density) and environment (e.g., climate, weather). NLP techniques could help at this point to mine social media and news articles to complement surveillance data and to gain an understanding of the sentiment of the population with respect to specific NPIs, while at the same time taking into consideration the biases of this type of data and the principally limited accuracy of text analytics as such. Altogether, further developments of modeling approaches are needed, which better combine data modalities across all relevant scales, i.e., ranging from the pathogen up to the environment level. This, however, will in turn require better availability, integration, and accessibility of necessary data, including electronic health records. The investment into such a data infrastructure is thus a prerequisite to making significant progress on the modeling side.

Models will only have an impact if they can support the human decision process. In recognition of this fact, several authors have tried to support scenario planning by associating NPIs with the predicted spatio-temporal development of the disease, or by forecasting healthcare resources and economic impact. While forecasts under the scenario of no further taken action might be improved by considering the aspects mentioned above for spatio-temporal modeling, predicting the effect of an NPI is principally challenged by several aspects: (i) The NPI could be new and thus there is no direct historical comparison, and (ii) there is always a lack of a proper control group, i.e., it is not possible to perform a study akin to a Randomized Clinical Trial. RL techniques are thus generally challenged by this inability to experiment with a new policy. It is thus unlikely that decision-makers would immediately trust the recommendation of an optimal NPI estimated by an RL algorithm. A better approach might hence be to offer a ranking of the predicted effectiveness of multiple NPIs together with the estimated economic costs, which should not be neglected.

Conclusion

In response to the ongoing COVID-19 pandemic, many countries currently review their strategies to be better prepared against future outbreaks. One important aspect in this context is to invest in data analytical capabilities, including modeling. Computational modeling approaches could help to earlier detect an outbreak, monitor the spatio-temporal spread, and to support the decision-making process by governmental authorities.

In this paper, we reviewed the diversity of existing modeling approaches for all three areas. Of course, each model is adjusted to a specific healthcare-related question by fitting it to particular data. In conclusion, models for early outbreak detection as well as spatio-temporal disease spread could be further improved by better combining and integrating data modalities across multiple scales. The ongoing COVID-19 pandemic in this context provides a "global laboratory" with the opportunity to retrospectively validate existing techniques as well as develop new ones. At the same, there is a need for funding bodies and governmental decision-makers to invest in corresponding data ecosystems. Models are likely to increase their impact on decision-making if they become more accurate and are at the same time explainable. Showing point estimates of a black-box model without highlighting epistemic uncertainties or providing further explanations of the most influential features is thus discouraged.

Author contributions

Conceptualization, methodology, supervision, project administration, and funding acquisition: HF. Data curation, formal analysis, visualization, investigation, validation, and writing—original draft: JB, DW, NL, SM, and HF. Writing—review and editing: JB, DW, NL, MG, NW, ET, LC, SM, and HF. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Authors NL, NW, and MG are employees of the commercial company Quinten-Health. Authors ET and LC are employees of the commercial company Sanofi. None of the afore mentioned companies had any influence on the scientific content presented in this paper.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The application value of the Modified Early Warning Score combined with age and injury site scores in the evaluation of injuries in emergency trauma patients

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Objective: To explore the application value of the Modified Early Warning Score (MEWS) combined with age and injury site scores in predicting the criticality of emergency trauma patients.

Methods: The traditional MEWS was modified by combining it with age and injury site scores to form a new MEWS combined scoring standard. The clinical data were collected from a total of 372 trauma patients from the emergency department of the Nantong First People's Hospital between June and December 2019. A retrospective analysis was conducted, and the patients were scored using the MEWS combined with age and injury site scores. The patients were grouped according to their prognoses and clinical outcomes. A statistical analysis was conducted based on the ranges of the combined scores, and the results of the combined scores of the different groups were compared.

Results: Among the 372 patients, the average score was 3.68 ± 1.25 points in the survival group, 8.33 ± 2.24 points in the death within 24 h group, and 8.38 ± 1.51 points in the death within 30 days of hospitalization group, and the differences were statistically significant ($p < 0.05$). The average score was 2.74 ± 0.69 points in the outpatient treatment group, 4.19 ± 0.72 points in the emergency stay group, 5.40 ± 0.70 points in the specialist inpatient group, 8.71 ± 2.31 points in the ICU group, and 7.82 ± 1.66 points in the specialist unplanned transfer to ICU group, with the differences between the groups being statistically significant ($p < 0.05$). The average length of hospital stay for patients with a joint score within the range of 6–8 points was 10.86 ± 2.47 days, with a direct ICU admission rate of 22.00% and an unplanned ICU admission rate of 16.00%. Patients with a joint score >8 points had an average length of hospital stay of 27.05 ± 4.85 days, with a direct ICU admission rate of 66.67% and an unplanned ICU admission rate of 33.33%.

Conclusion: Age and injury site are important high-risk indicators for trauma assessment, and using them in combination with the MEWS could improve the assessment of emergency patients with trauma, increasing the accuracy

of pre-screening triage and reducing rescue time. Therefore, this joint scoring method might be worthy of clinical promotion and application.

KEYWORDS

trauma, the Modified Early Warning Score, age, injury site, pre-screening triage

Introduction

Triage refers to the initial assessment of a patient's condition by the pre-screening triage nurse and the arrangement of appropriate medical treatment channels and treatment measures (1). Trauma is one of the important causes of human death, and it is currently the fourth cause of death among Chinese residents. The disability and fatality rate of people caused by trauma is still rising, and the success rate of trauma treatment in my country is much lower than that in developed countries (2). As more people have access to road transportation, road traffic accidents have increased, and trauma has become a major problem in emergency medical rescue. The Modified Early Warning Score (MEWS) system has been widely used in many countries because it is quick, easy, and practical (3–15). Scores are based on 5 items of body temperature, heart rate, consciousness, systolic blood pressure, and respiration. The higher the score, the more severe the disease, the higher the mortality rate and the ICU admission rate. MEWS $\geq$5 points often requires hospitalization; MEWS $\geq$9 points, the risk of death is significantly increased. However, the MEWS index only covers the most basic vital signs, and patients with severe trauma often have a combination of cranial, cervical, thoracic, abdominal, pelvic, and extremity injuries (16). Moreover, in clinical practice, age often determines the severity of the injury and the prognosis of a patient (3, 17). The present study was conducted to explore the establishment of a set of MEWS standards suitable for Chinese conditions. It is hoped that this will enable improvement in the accuracy of triage and the success rate of resuscitation of trauma patients in China, reduce the mortality and disability in these patients, and reduce the burden on affected families.

Subjects and methods

Subjects

Selected trauma patients in the emergency department of a tertiary hospital in Nantong City from June to December 2019 were the subjects for this study. Inclusion criteria were as follows: (1) trauma patients in the emergency department; (2) age $\geq$ 18 years; (3) complete medical records. Exclusion criteria were as follows: (1) patients who died before hospitalization or had undergone cardiopulmonary resuscitation; (2) patients with previous blood system diseases (such as anemia, leukemia, hemophilia, etc.).

Methods

The MEWS combined with age and injury site scores

In clinical investigations (16–21), age and the injury site have been found to be high-risk indicators in determining the severity of trauma. In this study, age and the injury site were divided into high to low thresholds, and the patient's scores for these two factors were added to the MEWS, forming a new rating scale. The details can be seen in Table 1.

Study methods

A retrospective study was used to collect data on emergency trauma patients from tertiary hospital in Nantong City in 2019. The included patients (according to the above criteria) were re-scored using the MEWS combined with age and injury site scores (hereinafter referred to as the "MEWS combined score" or "combined score"). The patients were grouped according to their different prognoses and outcomes. Based on the prognoses of patients, they were divided into the survival group and the death group; the death group was further divided into the death within 24 h group and the death within 30 days of hospitalization group. Based on the outcomes of patients, they were divided into the following five groups: outpatient treatment, emergency stay, specialist inpatient, ICU, and specialist unplanned transfer to ICU. The MEWS combined scores between different groups were compared, and the MEWS combined scores obtained by the patients were divided into intervals, and the average length of hospital stay, direct ICU admission rate, unplanned ICU admission rate, and emergency surgery rate of patients in different score ranges were statistically analyzed.

Statistical methods

The SPSS 21.0 software package was used for all data processing, and descriptive statistics were carried out. The measurement data were expressed as means $\pm$ standard deviations ($\bar{x} \pm s$), and the categorical data were expressed

TABLE 1 MEWS combined with age and injury site score.

Item	Score						
	3	2	1	0	1	2	3
Heart rate (times/min)		<40	41–50	51–100	101–110	111–130	>130
Systolic blood pressure (mmHg)	<70	71–80	81–100	101–199		≥200	
Respiration rate (times/min)		<9		9–14	15–20	21–29	≥30
Body temperature (°C)		<35		35–38.4		≥38.5	
Consciousness				Clear	Be responsive to sound	Be responsive to pain	No response
Age (year)				18–39	40–59	≥60	
Injury site		The chest and abdomen	The maxillofacial		The four extremities	The pelvis, spine	The brain

TABLE 2 General demographic information.

Age	Male	Female
18–39	65	46
40–59	88	50
≥60	70	53

as percentages (%). All continuous variables were tested for normality. The data were analyzed using the analysis of variance. The receiver operating characteristic (ROC) curve of the MEWS combined scores in predicting whether emergency trauma patients were hospitalized or not was drawn, and the area under the curve (AUROC) was calculated; $p < 0.05$ was considered statistically significant.

Results

General patient information

According to the criteria for inclusion and exclusion, 372 subjects were selected, including 223 males and 149 females, and the average age was 51.14 ± 17.34 years. There was no statistical difference in general patient data ($p > 0.05$) (Table 2).

The MEWS combined score

Among the 372 patients, the lowest combined score was 1 point, the highest was 16 points, and the average was 4.05 ± 1.82 points. There were 64 cases with a score of 0–2 points, accounting for 17.20%; 249 cases with a score of 3–5 points, accounting for 66.94%; 50 cases with a score of 6–8 points, accounting for 13.44%; and 9 cases with a score >8 points, accounting for 2.42%.

TABLE 3 Results of MEWS score in patients with different outcomes ($\bar{X}$ ± s, point).

Item	Number of cases (*n*)	The MEWS score	*F*	*p*
Survival	343	3.68 ± 1.25		
Death within 24 h	21	8.33 ± 2.24	163.05	<0.001
Death within 30 days of hospitalization	8	8.38 ± 1.51		

The combined score in patients with different prognoses

Among the study subjects, 343 cases survived, 21 cases died within 24 h, and 8 cases died within 30 days of hospitalization. The combined score in the survival group was significantly lower than that in the death group, and the difference was statistically significant ($p < 0.05$) (Table 3).

The combined score in patients with different outcomes

Among the 372 patients, the MEWS combined scores of the patients in the outpatient treatment group were the lowest, and the scores of the ICU inpatients were the highest. The combined scores of the five groups were significantly different ($p < 0.05$) (Table 4).

The comparison of the different combined score ranges

Among 372 patients, as the average hospital stay of the patients lengthened, the MEWS combined score gradually

TABLE 4 Results of MEWS score in patients with different referrals ($\bar{X} \pm s$, point).

Item	Number of cases (n)	The MEWS score	F	P
The outpatient	176	2.74 ± 0.69		
Kept observation in emergency department	79	4.19 ± 0.72		
The specialist hospitalization	89	5.40 ± 0.70	323.533	<0.001
ICU	17	8.71 ± 2.31		
The specialist unplanned transfer to ICU	11	7.82 ± 1.66		

increased; when the score was >8 points, the average hospitalization rate of patients was as high as 27.05 ± 4.85 points. Similarly, the higher the patient's direct ICU occupancy rate and the higher the emergency surgery rate, the higher the combined score (Table 5).

The predictive effect of the combined score with respect to patient admission

The area under the curve of MEWS combined score ROC was 0.92 (95% CI: 0.890, 0.950), and the combined score for determining whether a patient needed hospitalization was of statistical significance ($p < 0.05$), as shown in Figure 1. The predictive effects of different thresholds when hospitalization was taken as the predictive target are shown in Table 6.

Discussion

The application of the combined score in assessing the pre-screening triage of emergency trauma patients

With the development of society and the increasing renewal of means of transportation, trauma has become a major problem in emergency rescue work. In the process of treating trauma patients, the success rate of treatment is often decreased due to factors such as the high occultity of the trauma itself, rapid progress, and severe illness (22). Assessing patients' injuries and making accurate and reasonable judgments also greatly affects the success rate of trauma treatment (23). Trauma triage is not only based on vital signs, but also needs to assess high-risk factors such as age, injury site, injury mechanism, etc. Because the mechanism of injury cannot be obtained quickly, emergency triage often fails to provide targeted assessment. In a study by a Hong Kong scholar (24), the use of MEWS score can help junior nurses to observe the condition of patients. In this study, the score of age and injury site was added on the basis of traditional MEWS. According to the results, MEWS combined age, injury and injury the site score can preliminarily judge whether the patient's injury is life threatening, and the triage nurses can use this score as an evaluation tool when evaluating the condition of the trauma patients.

The application of the combined score in prognosis and outcome assessment of emergency patients with trauma

When the combined scores of the death within 24 h group and the death within 30 days of hospitalization group were compared, it was found that the combined score was higher in the former group than the latter. Of the patients in the five groups with different clinical outcomes, the patients in the outpatient treatment group had the lowest combined scores, while those in the direct ICU admission group had the highest scores. These results suggest that the combined score has some value in assessing the severity of the emergency in the trauma patient; this may assist the emergency resuscitation team in recognizing the patient's condition as quickly as possible and understanding the optimum time to implement resuscitation measures, as well as improving the success rate of patient resuscitation. In a study by Peng et al. (25), the MEWS was found to be of significant value when used to predict

TABLE 5 Comparison results of different MEWS score intervals.

Item	The average length of hospital stay (Day)	The ICU admission rate (%)		The rate of emergency surgery (%)
		The direct ICU admission rate	The unplanned transfer to ICU admission rate	
0–2 point	5.33 ± 1.27	0.00	0.00	0.00
3–5 point	9.18 ± 1.36	0.00	0.00	0.00
6–8 point	10.86 ± 2.47	22.00	16.00	28.00
>8 point	27.05 ± 4.85	66.67	33.33	77.78

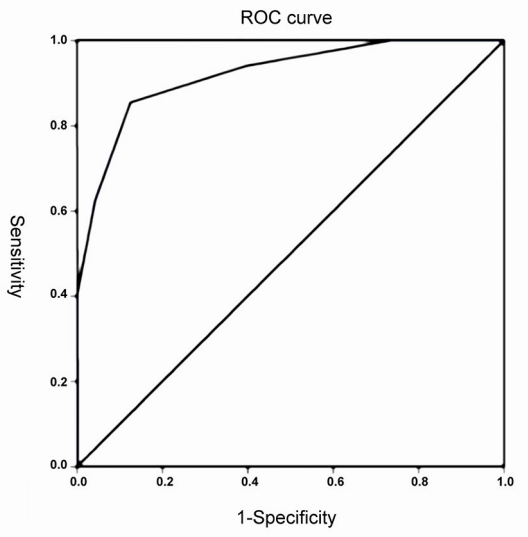

FIGURE 1
The receiver operating characteristic (ROC) curve of the Modified Early Warning Score (MEWS) combined score for predicting the hospitalization of patients.

TABLE 6 Comparison of predictive effect of different cut-off points on admission in the patients.

Item	Sensitivity (%)	1 - Specificity (%)	The youden index
1 point	100	94.50	0.055
2 point	100	73.30	0.267
3 point	94.00	39.20	0.548
4 point	85.50	12.50	0.730
5 point	62.40	4.30	0.581

the severity of the condition of non-trauma patients; their findings were similar to those of the present study, where it was found that combining the two factors of injury site and age with the MEWS is very effective in predicting the severity of the condition of trauma patients. The results of the comparison of the different ranges of the combined scores showed that a higher combined score was correlated with a longer length of hospital stay and higher ICU admission rate and was also positively correlated with the unplanned transfer to ICU admission rate and the emergency surgery rate. In a study by Liu et al. (26) to predict in-hospital mortality and ICU transfer in infected and non-infected patients, the MEWS score was the best choice. It can be seen that the MEWS combined score has guiding significance for the injury of trauma patients after hospitalization, and can be used as a further research direction.

The application of the combined score in the prediction of hospital admission of emergency patients with trauma

The merit of an evaluation system can be measured by plotting a ROC curve. In the present study, the AUROC was 0.92, indicating that the MEWS, combined with the age and injury site scores, has a high predictive value in determining hospital admission of emergency patients with trauma. The results were similar to the findings of Sun et al. (27), who added the two parameters of age and time of trauma to the MEWS, but the specificity of the evaluation in the present study was higher. It was found that the cutoff point of the MEWS for determining whether to admit an emergency trauma case was 5 points when Youden's index was calculated. When the MEWS, age, and injury site combined score in a trauma patient was $\geq$5 points, the hospitalization rate was higher, suggesting that the treatment pathway could be decided on and a reasonable treatment team allocated according to the situation when the patient arrives at the hospital.

The present study only investigated the specificity of the MEWS, age, and injury site combined score in the triage of trauma patients and the initial assessment of their condition. Although it could be inferred that a MEWS, age, and injury site combined score might be meaningful for guiding the assessment of injury in trauma patients after hospitalization, further investigations should be conducted to obtain more accurate scoring criteria for the follow-up assessment of hospitalized patients with trauma. These would be used in establishing a trauma scoring tool suitable for use in China so that the accuracy of triage and the success rate of treatment for trauma patients in China can be improved.

There are still many limitations in this research. Due to the impact of the COVID-19 epidemic in 2020, the study population selected for the present study was limited to patients who were hospitalized in 2019. At the same time, this current study only used the MEWS combined score for the preliminary assessment of the severity of the trauma in emergency patients and calculated the MEWS combined score to predict whether the trauma patient needed to be hospitalized. Furthermore, the specific criteria for the MEWS combined with the age and injury site scoring system still need to be explored and discussed. In addition, this study has not compared the MEWS combined score with the traditional MEWS and has not explored whether the MEWS combined score is more accurate and convenient than the traditional MEWS in clinical application. However, these issues can be explored in follow-up studies, as well as examining the assessment after trauma patients are hospitalized, in order to obtain more accurate scoring standards. This will provide a basis for establishing trauma scoring tools suitable for China's national conditions so as to improve the accuracy

of triage of trauma patients in China and the success rate of treatment.

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 study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the Nantong First People's Hospital. Written informed consent was obtained from all participants.

Author contributions

Y-FQ: conception, design of the research, analysis, and interpretation of the data. QL and D-FL: acquisition of data and statistical analysis. Y-QR: obtaining financing, writing of the manuscript, and critical revision of the manuscript for intellectual content. All authors have read and approved the final draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Development and validation of a nomogram for the early prediction of acute kidney injury in hospitalized COVID-19 patients

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Introduction: Acute kidney injury (AKI) is a prevalent complication of coronavirus disease 2019 (COVID-19) and is closely linked with a poorer prognosis. The aim of this study was to develop and validate an easy-to-use and accurate early prediction model for AKI in hospitalized COVID-19 patients.

Methods: Data from 480 COVID-19-positive patients (336 in the training set and 144 in the validation set) were obtained from the public database of the Cancer Imaging Archive (TCIA). The least absolute shrinkage and selection operator (LASSO) regression method and multivariate logistic regression were used to screen potential predictive factors to construct the prediction nomogram. Receiver operating curves (ROC), calibration curves, as well as decision curve analysis (DCA) were adopted to assess the effectiveness of the nomogram. The prognostic value of the nomogram was also examined.

Results: A predictive nomogram for AKI was developed based on arterial oxygen saturation, procalcitonin, C-reactive protein, glomerular filtration rate, and the history of coronary artery disease. In the training set, the nomogram produced an AUC of 0.831 (95% confidence interval [CI]: 0.774–0.889) with a sensitivity of 85.2% and a specificity of 69.9%. In the validation set, the nomogram produced an AUC of 0.810 (95% CI: 0.737–0.871) with a sensitivity of 77.4% and a specificity of 78.8%. The calibration curve shows that the nomogram exhibited excellent calibration and fit in both the training and validation sets. DCA suggested that the nomogram has promising clinical effectiveness. In addition, the median length of stay (m-LS) for patients in the high-risk group for AKI (risk score $\geq$ 0.122) was 14.0 days (95% CI: 11.3–16.7 days), which was significantly longer than 8.0 days (95% CI: 7.1–8.9 days) for patients in the low-risk group (risk score $<$0.122) (hazard ratio (HR): 1.98, 95% CI: 1.55–2.53, $p < 0.001$). Moreover, the mortality rate was also significantly higher in the high-risk group than that in the low-risk group (20.6 vs. 2.9%, odd ratio (OR):8.61, 95%CI: 3.45–21.52).

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Conclusions: The newly constructed nomogram model could accurately identify potential COVID-19 patients who may experience AKI during hospitalization at the very beginning of their admission and may be useful for informing clinical prognosis.

KEYWORDS

COVID-19, acute kidney injury, nomogram, mortality, length of stay

Introduction

In December 2019, Wuhan, China, reported the emergence of new coronavirus-associated pneumonia brought on by the novel SARS-CoV-2 infection (1, 2). On February 12, 2020, the World Health Organization (WHO) formally identified it as coronavirus disease 2019 (COVID-19), and on March 11, 2020, it was deemed a global pandemic. As of March 30, 2022, 227 countries and territories have been affected worldwide, with cumulatively more than 485 million cases confirmed, with over 6 million deaths (3). The main clinical feature of COVID-19 is acute respiratory symptoms (1, 2, 4, 5). Depending on the severity of the disease, patients can present with mild infections with no symptoms; moderate infections with symptoms such as fever, cough, and dyspnea; or even severe infections with acute respiratory distress syndrome (ARDS) (6, 7).

Although COVID-19 is a respiratory illness, it often results in multisystem damage that further progresses to multiple organ failure (MODS) and even, in severe cases, to patient death (4–7). The kidney is an important target organ for COVID-19 infection, and viral invasion causes acute kidney injury (AKI) through direct attack, an inflammatory storm, and inflammatory cell infiltration (8–10). The global incidence of COVID-19 in combination with AKI ranges from 0. 5 to 80%, and the incidence of AKI in the intensive care unit (ICU) ranges from 6 to 80% (11). The incidence of AKI significantly increases after COVID-19 infection (10, 12, 13). Studies have revealed that, compared to those hospitalized for non-COVID-19 reasons, COVID-19-infected hospitalized patients have an increased prevalence of AKI (31.0 vs. 18.0%) (14). A meta-analysis of 13,137 patients showed that the incidence of AKI in patients with COVID-19 was 17% (11). While, two observational studies that included 6,477 and 5,216 patients, respectively, revealed that the incidence of AKI among hospitalized COVID-19 patients was as high as 32 and 37% (15, 16). AKI increased the frequency and risk of mechanical ventilation in COVID-19 patients and lengthened their hospital stays. In addition, close to half of AKI patients did not have full recovery of renal function to baseline on discharge (16). Moreover, the incidence of AKI is linked with hospital mortality in patients with COVID-19 infection and is an independent risk factor for poor prognosis in critically ill patients (10, 12, 13, 17). A study that included 3,099 adult patients in critical condition who had COVID-19 showed that 20.6% of patients had to undergo kidney replacement therapy (KRT) for severe AKI within 14 days of entry to the intensive care unit. On day 28, the overall mortality rate for these patients was 54.9%, and up to 63.3% by the time of the last follow-up (17 days). Even among patients who were eventually discharged with a cure, there were still 33.6% of them dependent on KRT at discharge, and more than 50% of these patients still relied on KRT for the following 2 months (18). An autopsy study of patients who died from COVID-19 revealed that AKI was observed in 93.9% of patients, and 62% of patients experienced acute tubular necrosis of a different degree (14). Therefore, early clinical identification of patients who are at high risk for AKI could optimize the allocation of medical resources and enhance intervention management, thereby improving prognosis and reducing mortality.

Hence, we aimed to apply a new method to establish and validate a simple-to-use and effective early prediction model for AKI in hospitalized COVID-19 patients based on clinical characteristics, past medical history, clinical symptoms, signs, and key laboratory biochemical indicators. The model could help clinicians to screen patients with COVID-19 for the risk of AKI to identify and intervene in the early development of AKI. Furthermore, we investigated the prognostic differences between patients with high- and low-risk AKI based on predictive models.

Methods

Data collection and study design

Data from 480 COVID-19-positive patients were obtained from the public database of the Cancer Imaging Archive (TCIA) (collection of COVID-19-NY-SBU). This collection of patients was acquired at Stony Brook University with associated clinical data. AKI was defined as: (1) An increase in serum creatinine of 0.3 mg/dL within 48 h; (2) A rise in serum creatinine that is known or suspected to have happened within the previous 7 days, increasing it to 1.5 times baseline (or 50% above baseline); (3) Urine volume <0.5 ml/kg/h for 6 h. The inclusion criteria are as follows: (1) Age ≥ 18 years (weight $\geq$ 35Kg); (2)

Laboratory-confirmed COVID-19 [positive polymerase chain reaction (PCR)]; (3) Expected hospital stay longer than 48 h; (4) With complete clinical information and laboratory test results. The exclusion criteria are as follows: (1) The Previous history of confirmed COVID-19. (2) The patient has received prophylactic treatment for COVID-19 within the last 30 days. (3) Patients with underlying renal disease such as chronic renal failure or post-transplantation or those on continuous renal replacement therapy, hemodialysis, or peritoneal dialysis. (4) Other diseases that may affect kidney function, such as tuberculous kidney disease, immune nephritis, and kidney tumors. (5) Presence of other serious diseases that damage life expectancy, such as acute myocardial infarction, cerebral hemorrhage, and pulmonary embolism. (6) Pregnancy and breastfeeding. The following information was collected for each patient: (1) general clinical characteristics of age, gender, and smoking history; (2) past medical history of hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and other lung diseases; (3) home medication history of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), antibiotics, and non-steroidal anti-inflammatory drugs (NSAID); (4) clinical symptoms of fever, cough, dyspnea, vomiting, diarrhea, and abdominal pain; (5) signs of oral temperature, arterial oxygen saturation (SaO2), respiratory rate, heart rate, systolic blood pressure, and mean blood pressure; (6) laboratory indicators of leukocyte count, neutrophils count, lymphocytes count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), procalcitonin (PCT), C-reactive protein (CRP), sodium, potassium, chloride, lactate, blood urea nitrogen (BUN), serum creatinine (SCR), glomerular filtration rate (GFR), and glucose. All cohort patients were randomly divided into two sets at a ratio of 7:3: the training set was used to construct the prediction model, and the validation set was used to evaluate the performance of the model. The study was approved by the Ethics Committee of Yantai Yuhuangding hospital and conducted in accordance with the ethical principles of the Declaration of Helsinki. As all of the data in this work were retrieved from free online databases, informed consent was waived.

Element selection and construction of the nomogram

The least absolute shrinkage and selection operator (LASSO) regression method was utilized in the training set in order to eliminate potentially predictive elements for AKI. LASSO regression analysis was performed to gain refinement of the model by constructing a penalization function, and applicable to regression analysis of high-dimensional data with multiple covariates. In the process of parameter selection, the LASSO regression automatically shrinks the regression coefficients of 41 parameters using the penalty parameter lambda (λ). The larger the value of lambda (λ), the more the coefficients of the parameters shrink to zero. Consequently, some parameters are eliminated due to the narrowing of their coefficients to near zero, while the remaining parameters are ultimately selected. Cross-validation was adopted to validate the adjustment parameter lambda (λ) appropriateness for the LASSO regression. The lambda (λ) parameter with minimum criteria of mean-squared error was selected to screen the potential predictive elements. Factors screened in LASSO regression were subsequently analyzed in a multivariate logistic regression model to identify significant predictors of AKI in hospitalized COVID-19 patients. To avoid overfitting, elements in the multivariate logistic regression model with a p-value < 0.1 were used to construct the prediction nomogram.

Validation of the nomogram

Boost bootstrapping validation (1,000 bootstrap resamples) was used to evaluate the predictive effectiveness of the nomogram model in both the training- and validation sets. The performance metrics include the receiver operating curves (ROC), calibration curves, as well as decision curve analysis (DCA). The ROC and corresponding area under the curve (AUC) were utilized to quantify the discriminatory ability of the AKI nomogram. The AUC can be calculated by the integration of the area under the line segments, it ranges from 0.5 to 1.0, with 0.5 indicating a random and 1.0 indicating a perfectly differentiated. To evaluate the nomogram's identification and calibration, calibration curves were constructed. The Hosmer–Lemeshow test was performed to estimate the goodness-of-fit of the nomogram. To assess the nomogram model's clinical applicability and overall benefit, decision curve analysis (DCA) was utilized. DCA is an efficacious approach to the evaluation of the clinical benefits of alternative models, and when employed in nomograms, it can quantify the net benefits by performing at variable threshold probabilities. The DCA plotted the all-patient treatment scenario and the no-patient treatment scenario as two reference curves. The net benefit was calculated by deducting false-positive patients from true-positive patients, weighted by the potential damage of going untreated vs. the detrimental effects of going needless treatment. When the decision curve reveals that the nomogram is of greater benefit than the all-patient treatment scenario and the no-patient treatment scenario, it would indicate that the nomogram is clinically valid.

Nomogram-based risk-group stratification

Based on the nomogram, risk scores for AKI were calculated for each patient, and patients were then divided into high- and

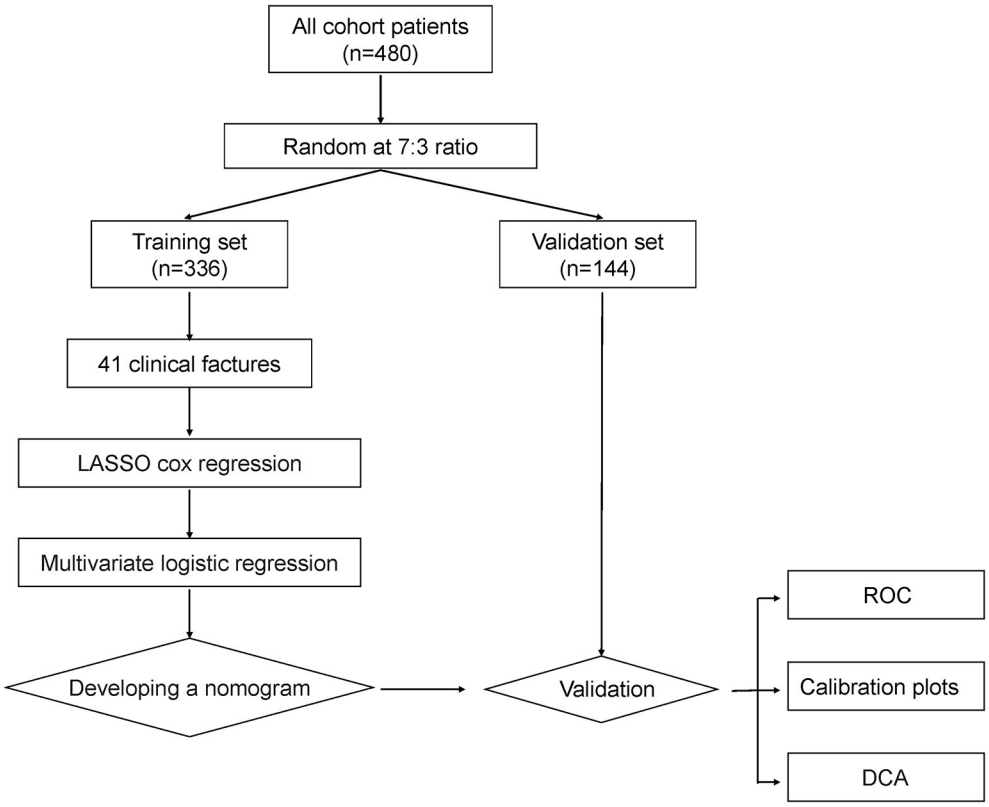

FIGURE 1
The flowchart of the study procedure. Abbreviations: LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic; DCA, decision curve analysis.

low-risk cohorts based on the optimal cutoff value determined by the Youden index from the ROC analysis of the training set. Differences in length of stay and last status (discharged or deceased) of patients in the high- and low-risk cohorts were compared in both training and validation sets, respectively.

Statistical analysis

The categorical variables were compared using Pearson's chi-square test and presented as percentages (%). For continuous variables, the Shapiro-Wilk test was used to test for normality, if the variables were normally distributed, the mean (standard deviation) was used for statistical description and the *t*-test was used for comparison between groups; otherwise, the medians [interquartile ranges (IQRs)] was used for statistical description and the Mann–Whitney *U*-test was used for comparison between groups. The median length of stay (m-LS) was calculated using the Kaplan-Meier approach, and the log-rank test was utilized to compare differences between high-risk and low-risk groups. The Cox proportional hazards model was used to determine the hazard ratio (HR) and its associated 95% confidence interval (CI). The mortality rate was compared by Fisher's exact or chi-squared tests, and odds ratios (ORs) with 95% CIs were calculated by logistic regression models. Statistical analysis was performed with the SPSS program (V22.0, Inc., Chicago, IL, USA) and R project (version 4.1.3, "glmnet" packages for LASSO logistic regression analysis, "forestplot" packages for plot forest, "hmisc" package for plot nomogram, "calibration curves" package for plot calibration curves, "pROC" package for plot ROC curves and calculate AUCs, and "stdca" package for DCA). A p-value < 0.05 (two-sided) was considered statistically significant.

Results

Characteristics of patients

In total, 480 patients with COVID-19-positive were included in this study; 336 were randomized into the training set, while the remaining 144 were randomized into the validation set. The flowchart of the study procedure was present in Figure 1. The baseline characteristics of the two sets of patients were essentially balanced. The incidence of AKI was 17.7% (85 of 480) in the

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TABLE 1 Baseline characteristics of patients in training set, validation set and all populations.

Characteristic	All patients ($n = 480$)	Training set ($n = 336$)	Validation set ($n = 144$)	P value
Age				
≥60	224 (46.7%)	153 (45.5%)	71 (49.3%)	0.448
<60	256 (53.3%)	183 (54.5)	73 (50.7%)	
Gender				
Male	300 (62.5%)	204 (60.7%)	96 (66.7%)	0.217
Female	180 (37.5%)	132 (39.3%)	48 (33.3%)	
Smoking				
Yes	123 (25.6%)	82 (24.4%)	41 (28.5%)	0.350
No	357 (74.4%)	254 (75.6%)	103 (71.5%)	
Hypertension				
Yes	236 (49.2%)	173 (51.5%)	63 (43.8%)	0.120
No	244 (50.8%)	163 (48.5%)	81 (56.2%)	
Diabetes				
Yes	130 (27.1%)	87 (25.9%)	43 (29.9%)	0.370
No	350 (72.9%)	249 (74.1%)	101 (70.1%)	
CAD				
Yes	58 (12.1%)	40 (11.9%)	18 (12.5%)	0.855
No	422 (87.9%)	296 (88.1%)	126 (87.5%)	
COPD				
Yes	18 (3.8%)	11 (3.3%)	7 (4.9%)	0.402
No	462 (96.2%)	325 (96.7%)	137 (95.1%)	
OLD				
Yes	72 (15.0%)	44 (13.1%)	28 (19.4%)	0.074
No	408 (85.0%)	292 (86.9%)	116 (80.6%)	
Malignancies				
Yes	37 (7.7%)	29 (8.6%)	8 (5.6%)	0.247
No	443 (92.3%)	307 (91.4%)	136 (94.4%)	
ACEI				
Yes	72 (15.0%)	47 (14.0%)	25 (17.4%)	0.343
No	408 (85.0%)	289 (86.0%)	119 (82.6%)	
ARB				
Yes	72 (15.0%)	53 (15.8%)	19 (13.2%)	0.468
No	408 (85.0%)	283 (84.2%)	125 (86.8%)	
Antibiotic				
Yes	139 (29.0%)	92 (27.4%)	47 (32.6%)	0.244
No	341 (71.0%)	244 (72.6%)	97 (67.6%)	
NSAID				
Yes	39 (8.1%)	305 (90.8%)	136 (94.4%)	0.177
No	441 (91.9%)	31 (9.2%)	8 (5.6%)	
Fever				
Yes	395 (82.3%)	277 (82.4%)	118 (81.9%)	0.896
No	85 (17.7%)	59 (17.6%)	26 (18.1%)	
Cough				
Yes	402 (83.8%)	281 (83.6%)	121 (84.0%)	0.914
No	78 (16.3%)	55 (16.4%)	23 (16.0%)	
Dyspnea				
Yes	370 (77.1%)	252 (75.0%)	118 (81.9%)	0.095
No	110 (22.9%)	84 (25.0%)	26 (18.1%)	

(Continued)

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TABLE 1 (Continued)

Characteristic	All patients ($n = 480$)	Training set ($n = 336$)	Validation set ($n = 144$)	P value
Vomiting				
Yes	89 (18.5%)	64 (19.0%)	25 (17.4%)	0.663
No	391 (81.5%)	272 (81.0%)	119 (82.6%)	
Diarrhea				
Yes	191 (39.8%)	141 (42.0%)	50 (34.7%)	0.137
No	289 (60.2%)	195 (58.0%)	94 (65.3%)	
Abdominal pain				
Yes	65 (13.5%)	49 (14.6%)	16 (11.1%)	0.308
No	415 (86.5%)	287 (85.4%)	128 (88.9%)	
T				
(°C)	37.50 (37.00, 38.30)	37.60 (37.10, 38.40)	37.40 (37.00, 38.10)	0.157
SaO2				
	94.00 (91.00, 96.00)	94.00 (91.00, 96.00)	93.00 (91.00, 96.00)	0.209
PR				
(#/min)	20.00 (18.00, 24.00)	20.00 (18.00, 24.00)	20.00 (18.00, 25.00)	0.811
HR				
(#/min)	100.00 (88.00, 112.00)	100.00 (88.00, 113.00)	99.00 (88.00, 111.00)	0.484
SBP				
(mmHg)	125.00 (113.00, 142.00)	125.00 (112.00, 142.00)	125.00 (113.00, 141.00)	0.944
MAP				
(mmHg)	91.00 (84.00, 99.00)	91.00 (82.00, 98.00)	91.00 (85.00, 99.00)	0.469
Leukocytes				
(#/volume)	6.83 (5.22, 8.81)	6.69 (5.21, 8.72)	7.44 (5.50, 9.10)	0.108
Neutrophils				
(#/volume)	5.27 (3.84, 7.14)	5.12 (3.76, 6.98)	5.69 (4.08, 7.33)	0.071
Lymphocytes				
(#/volume)	0.93 (0.67, 1.25)	0.93 (0.66, 1.25)	0.94 (0.67, 1.25)	0.985
AST				
(U/volume)	42.00 (29.00, 64.00)	42.00 (30.00, 63.00)	42.00 (28.00, 66.00)	0.715
ALT				
(U/volume)	33.00 (22.00, 55.00)	33.00 (22.00, 55.00)	33.00 (21.00, 55.00)	0.731
PCT				
(moles/volume)	0.16 (0.10, 0.29)	0.16 (0.10, 0.30)	0.16 (0.09, 0.28)	0.768
CRP				
(moles/volume)	8.60 (3.80, 14.20)	8.60 (4.00, 14.40)	8.70 (3.60, 14.00)	0.663
Sodium				
(moles/volume)	136.00 (133.00, 138.00)	136.00 (133.00, 138.00)	136.00 (133.00, 139.00)	0.312
Potassium				
(moles/volume)	4.10 (3.80, 4.40)	4.10 (3.80, 4.40)	4.20 (3.80, 4.50)	0.164
Chloride				
(moles/volume)	97.00 (94.00, 99.00)	97.00 (94.00, 99.00)	98.00 (94.00, 99.00)	0.403
Lactate				
(moles/volume)	1.40 (1.10, 1.80)	1.40 (1.10, 1.80)	1.50 (1.10, 1.80)	0.514
Bicarbonate				
(moles/volume)	24.00 (22.00, 25.00)	24.00 (22.00, 25.00)	24.00 (22.00, 26.00)	0.183
BUN				

(Continued)

TABLE 1 (Continued)

Characteristic	All patients ($n = 480$)	Training set ($n = 336$)	Validation set ($n = 144$)	P value
(mass/volume)	13.00 (10.00, 20.00)	13.00 (9.00, 20.00)	14.00 (11.00, 21.00)	0.368
SCR				
(mass/volume)	0.91 (0.72, 1.16)	0.89 (0.70, 1.13)	0.98 (0.77, 1.27)	0.043
GFR				
(ml/min)	0.91 (0.72, 1.16)	0.89 (0.70, 1.13)	0.98 (0.77, 1.27)	0.213
Glucose				
(mass/volume)	120.00 (107.00, 151.00)	120.00 (106.00, 147.00)	121.00 (110.00, 159.00)	0.181
AKI	17.7%	16.1%	21.5%	0.151

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; OLD, other lung diseases including asthma; ACEI, angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug; T, temperature; SaO2, artery oxygen saturation; PR, respiration rate; HR, heart rate; SBP, systolic blood pressure; MAP, mean blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PCT, procalcitonin; CRP, C-reactive protein; BUN, blood urea nitrogen; SCR, serum creatinine; GFR, glomerular filtration rate.

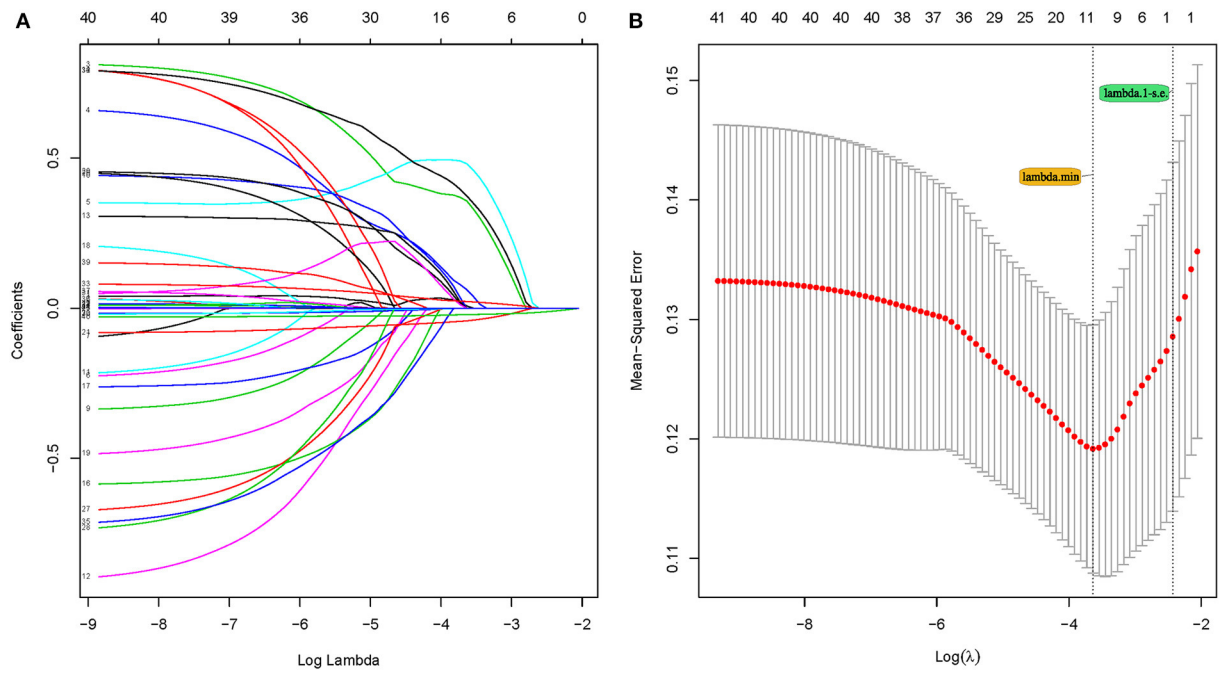

FIGURE 2
Feature selection using the least absolute shrinkage and selection operator (LASSO) Cox regression model. **(A)** LASSO coefficient profiles of the 41 features. **(A)** coefficient profile plot was produced against the log (λ) sequence. **(B)** Selection of tuning parameter (λ) in the LASSO regression using 10-fold cross-validation *via* minimum criteria. At the optimal values log (λ), where features are selected, two dotted vertical lines were drawn at the optimal scores by minimum criteria and 1-s.e. criteria.

overall population, 16.1% (54 of 336) in the training set, and 21.5% (31 of 144) in the validation set, respectively (Table 1). Supplementary Table 1 compares the baseline characteristics of patients with AKI and those without AKI. For the whole cohort, there were slightly more patients aged <60 years (256, 53.3%) than those aged ≥60 years (224, 46.7%). There were 300 male patients (62.5%), which was more than the number of female patients (180, 37.5%). The majority of patients presented with infectious and respiratory symptoms, of which 395 (82.3%) patients presented with fever, 402 (83.8%) with cough, and 370 (77.1%) with dyspnea, while there was a relatively low frequency of gastrointestinal symptoms. Of those 480 patients, 21 patients received kidney replacement therapy, and 14 received kidney transplants. For patients receiving kidney replacement therapy, the mortality rate was 52.4% (11 of 21) and the mean length of stay was 39 days (only for discharged patients). For patients receiving received a kidney transplant, the mortality rate was 0.00% with a mean length of stay was 14.6 days. The baseline

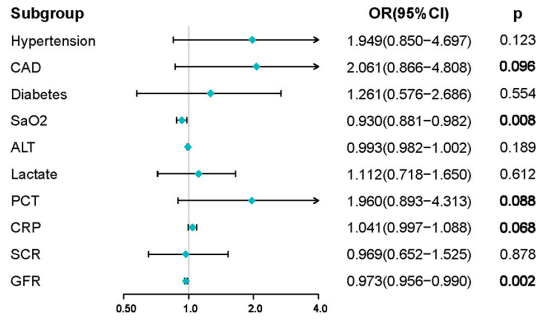

FIGURE 3
Results of multivariate logistic regression analysis in the training set. Factors with p-values < 0.1 were screened for constructing the nomogram model. Abbreviations: CAD, coronary artery disease; SaO2, artery oxygen saturation; ALT, alanine aminotransferase; PCT, procalcitonin; CRP, C-reactive protein; GFR, SCR, serum creatinine; GFR, glomerular filtration rate.

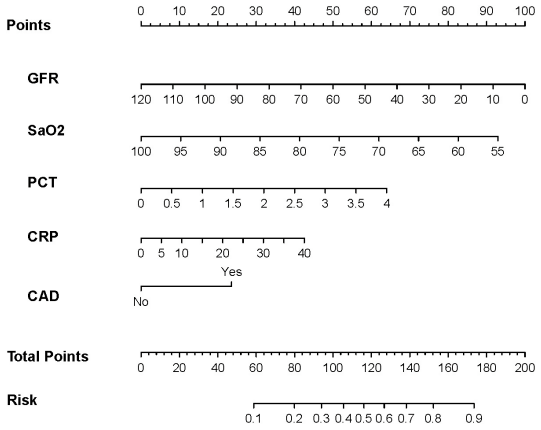

FIGURE 4
The nomogram was developed in the training set. It included five factors: glomerular filtration rate (GFR), artery oxygen saturation (SaO2), procalcitonin (PCT), C-reactive protein (CRP), and history of coronary artery disease (CAD). The nomogram plot provides a visual way to predict the risk of AKI for COVID-19 patients.

information for patients, including laboratory indicators, is detailed in Table 1.

Feature selection

Feature selection was performed in the training set, and 41 parameters were included in the LASSO logistic regression analysis for predictor screening. The coefficient profile plot was produced against the log (λ) sequence (Figure 2A). Minimum criteria are used to select the tuning parameter (λ) for the LASSO regression utilizing 10-fold cross-validation. The results show that the optimal value of tuning parameter λ in the LASSO logistic regression was 0.026 when the mean-squared error reached its minimum value. Ten parameters with non-zero coefficients were screened: hypertension history, CAD, diabetes, SaO2, ALT, lactate, PCT, CRP, SCR, and GFR (Figure 2).

Construction of the nomogram and performance examination

The parameters screened in the LASSO regression were utilized for the multivariate logistic regression model analysis, and the results demonstrated that only SaO2 and GFR were independent predictors of the occurrence of AKI (SaO2, OR:0.930, 95% CI: 0.881–0.982, $P = 0.008$; GFR, OR:0.973, 95% CI: 0.956–0.990, $P = 0.002$) (Figure 3). However, to avoid overfitting of the nomogram model, parameters with $p < 0.1$ were selected for model construction. Finally, a predictive nomogram model for the occurrence of AKI in hospitalized COVID-19 patients based on CAD, SaO2, PCT, CRP, and GFR was constructed (Figure 4, Supplementary Table 2). Based on the nomogram, the point scale scores for these five independent variables could be calculated for each patient, and their sum was the total point value. The ROC curve showed that the nomogram had favorable discrimination for AKI, with an AUC of 0.831 (95% CI: 0.774–0.889), a sensitivity of 85.2%, and a specificity of 69.9% (Figure 5A), which was significantly better than those of SCR and BUN (Supplementary Figure 1A). The calibration curves visually revealed favorable accordance between the prediction of the nomogram and the actual observations (Figure 5B). The Hosmer–Lemeshow test demonstrated a nice goodness-of-fit of the nomogram, with no significant differences observed ($p = 0.247$). DCA showed that the nomogram had a nice overall net benefit in the threshold probability range of 16–63%, and was superior to those of SCR and BUN (Supplementary Figure 1C), indicating that the model has promising clinical effectiveness (Figure 5C).

Validation of the nomogram

Next, we evaluated the effectiveness of the model in the validation set. Consistent with the results of the training set, the nomogram yielded a favorable AUC of the ROC curve of 0.810 (95% CI: 0.737–0.871), with a sensitivity of 77.4% and specificity of 78.8% (Figure 5D), better than those of SCR and BUN (Supplementary Figure 1B). The calibration curve and Hosmer–Lemeshow test suggested that the nomogram had good calibration and fit in the validation set ($p = 0.247$) (Figure 5E). Moreover, DCA visually revealed that the nomogram had an overall net benefit within a wider threshold probability in the validation set (Figure 5F, Supplementary Figure 1D). These

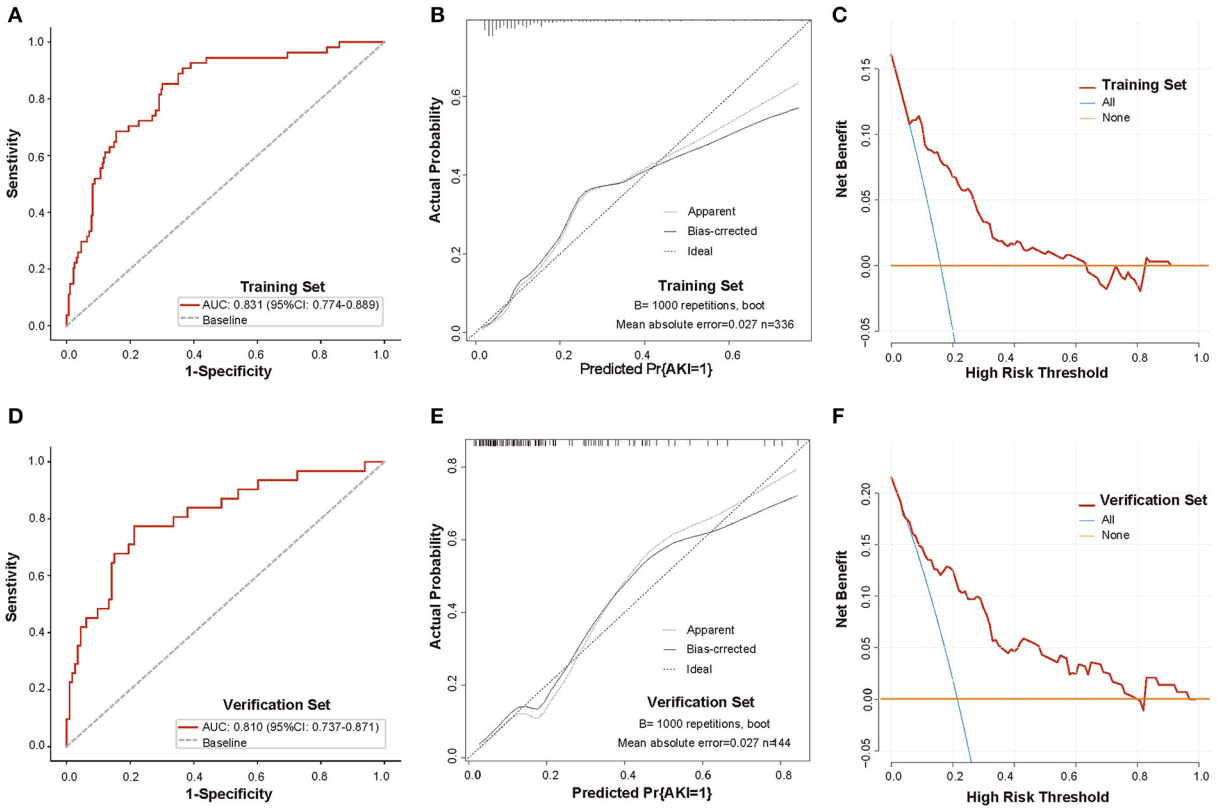

FIGURE 5
Validation of the discrimination power of the nomogram in the training and validation sets. **(A,D)** ROC curve analysis of the nomogram in the training and validation sets (AUC, 0.831 and 0.810, respectively); **(B,E)** Calibration plot of the nomogram in the training and validation sets, The black dashed diagonal line indicates the perfect prediction of the ideal model. The solid black line represents the performance of the nomogram, and the closer the fit to the diagonal line, the more accurate the prediction. The gray dashed line represents the performance of the model trained after bootstrapping validation (1,000 bootstrap resamples), which corrects the overfitting situation; **(C,F)** DCA analysis of the nomogram in the training and validation sets. The y-axis represents the net benefit, the x-axis represents the threshold probability. The red line represents the nomogram, and the blue and orange lines represent the all-patient treatment scenario and the no-patient treatment scenario, respectively. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

results suggest that the nomogram functions well and has excellent predictive power for the validation set.

Nomogram-based risk stratification

Based on the nomogram constructed in the training set, the probability of occurrence of AKI was calculated for each patient. Using the optimal cutoff value of 0.122 obtained from the ROC analysis of the training set, the two sets of patients were subsequently classified into high- and low-risk groups. In the training set, there were 205 patients in the low-risk group and 131 patients in the high-risk group. The median length of stay (m-LS) for patients in the high-risk group was 14.0 days (95% CI: 11.3–16.7 days), which was significantly longer than 8.0 days (95% CI: 7.1–8.9 days) for patients in the low-risk group, which was (HR:1.98, 95%CI: 1.55–2.53, $p < 0.001$) (Figure 6A). Similarly, in the validation set, we also observed a significantly longer length of stay in the high-risk group than in the low-risk group (m-LS: 17.0 days vs. 8.0 days, HR: 2.10, 95% CI: 1.45–3.05, $p < 0.001$) (Figure 6B). In addition, we found that the mortality rate was higher in the high-risk group. In the training set, there were 27 patients in the high-risk group having a last status of death, with a mortality of 20.6%, compared to 2 (2.9%) in the low-risk group in the training set (OR: 8.61, 95% CI: 3.45–21.52, $p < 0.001$). The results from the validation set corroborated this finding, where the last status was deceased in 14 (23.3%) and 2 (2.4%) patients in each of the high- and low-risk groups, respectively, with statistically significant differences (OR: 12.48, 95% CI: 2.72–57.33, $p = 0.001$). These results indicate that the nomogram model can be applied to predict the prognosis of hospitalized COVID-19 patients (Table 2).

Discussion

In this study, we developed a predictive nomogram model for acute kidney injury in hospitalized COVID-19 patients based

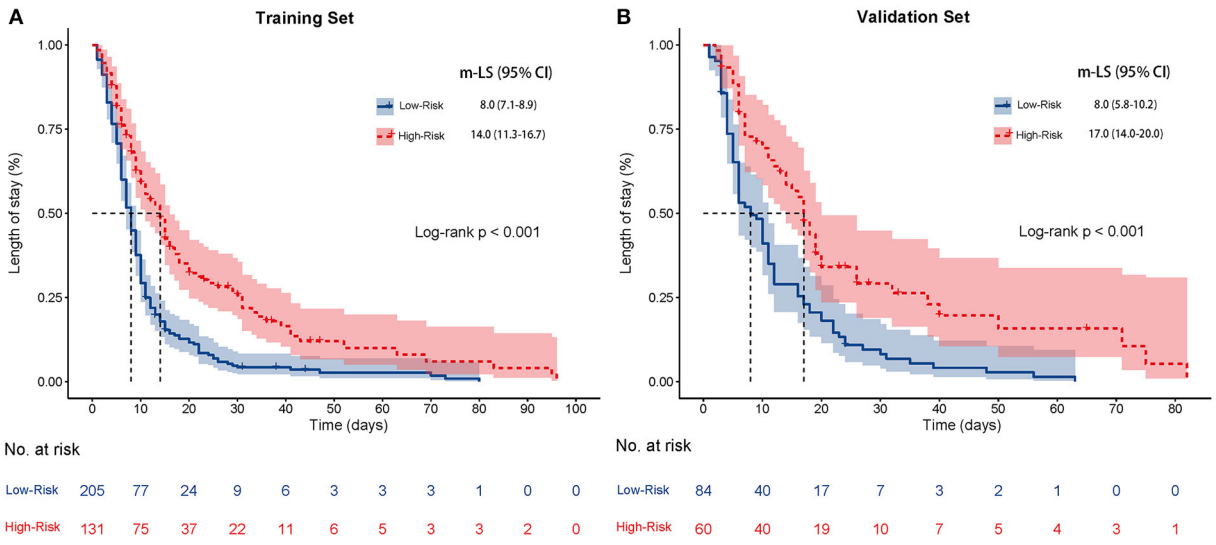

FIGURE 6
Kaplan-Meier curves for the length of stay of high-risk patients and low-risk patients based on the optimal segmentation threshold obtained from the ROC analysis in the training set **(A)** and the validation set **(B)**. Abbreviations: m-LS: median length of stay.

on SaO2, PCT, CRP, GFR, and the history of CAD. It is an easy-to-use, well-performing nomogram model with promising discrimination, predictive accuracy, and clinical practical utility. In addition, the risk score based on the nomogram was related to the length of stay and the last status of the patient. This is the first nomogram model to predict AKI in COVID-19 inpatients at an early stage. It is conducive to the early identification of high-risk patients with AKI to provide early intervention and treatment, and it can effectively and reasonably optimize the allocation and utilization of hospital beds as well as medical resources, thereby alleviating the shortage of medical resources and improving patient prognosis.

Acute kidney injury is a group of clinical syndromes characterized by a rapid decline (hours to days) in kidney function (19) and is a common complication in patients hospitalized with COVID-19 (8–10, 12, 13, 17). Patients may present with urinary abnormalities, for example, proteinuria and hematuria, elevated blood creatinine and urea nitrogen, and even positivity for SARS-CoV-2 in urine tests (1, 2, 10, 13). According to previous studies, ∼40% of patients with COVID-19 had proteinuria on admission, ∼10% had elevated blood creatinine during the course of the disease, ∼21% had elevated blood urea nitrogen, ∼43% had persistently elevated blood urea nitrogen, ∼63% had proteinuria, and ∼26.9% had hematuria (20, 21). The incidence of AKI varied by medical center, race, statistical size of the sample, and severity of disease in the included population. For example, According to a study of 138 Wuhan residents who were diagnosed with COVID-19, the incidence of AKI was 3.6%, while the incidence of AKI in critically ill patients was 8.3% (2). Of 1,099 patients with COVID-19, Guan et al. (4) reported an incidence of AKI of 0.5%, with 5 of 17 (2.9%) critically ill patients developing AKI. In addition, another Chinese study enrolled 710 patients with COVID-19, 52 of whom were critically ill adults, with an AKI rate of 29% (21). An Italian study showed a 15% incidence of AKI in COVID-19 patients (22), and the results of another study of 5,700 patients with COVID-19 in New York reported an AKI incidence reaching as high as 22.2% (23). Altogether, the incidence of AKI in patients with COVID-19 ranges from 0.1 to 56.9%, while it reaches 77% in patients with severe COVID-19 (2, 4, 11, 21–23). Analyzing the previous evidence, the following information can be obtained. First, kidney injury is not uncommon in patients with COVID-19 (especially those with severe disease). Second, the incidence of AKI has been inconsistent, which is mainly related to the sample size and study population, and the incidence of AKI is higher in severe and critical COVID-19 patients. Most importantly, COVID-19 complicated with AKI is an independent risk factor for poor prognosis (11, 21–23). Among patients who died from COVID-19, the incidence of AKI was as high as 37.5%, which was significantly higher than the 15% of surviving cases (24). The mortality rate of COVID-19 patients complicated with AKI was reported to be 67% (95% CI: 39.8–86.2%), and the risk of death was 13 times that of patients without AKI (OR = 13.3, 95% CI: 6.1–29.2) (25). In addition, the severity of AKI is associated with patient prognosis, and patients with the late-stage disease have a significantly higher risk of death (2, 8, 10, 12). Therefore, early assessment of AKI risk is important to guide physicians to intervene early and prevent AKI, protect renal function, and avoid progression of the patient's condition.

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TABLE 2 Comparisons of last status and length of stay of patients on Nomogram-based risk stratification in training and validation set.

Characteristics	No.	Last status					Length of stay (days)		
		Deceased	Discharged	Mortality	OR (95%CI)	*P*	m-LS (95%CI)	HR (95%CI)	*P*
Training set									
High-risk	131	27	104	20.6%	8.61 (3.45–21.52)	<0.001	14.0 (11.3–16.7)	1.98 (1.55–2.53)	<0.001
Low-risk	205	6	199	2.9%			8.0 (7.1–8.9)		
Validation Set									
High-risk	60	14	46	23.3	12.48 (2.72–57.33)	0.001	17.0 (14.0–20.0)	2.10 (1.45–3.05)	<0.001
Low-risk	84	2	82	2.4%			8.0 (5.8–10.2)		

A nomogram may provide a quantitative and pragmatic predictive tool for risk stratification of COVID-19 patients for the development of AKI during hospitalization. In this study, GFR, SaO2, PCT, CRP, and history of CAD were selected by LASSO and multivariate regression for the construction of the predictive nomogram model of AKI. These factors have been demonstrated to correlate with the development of AKI in previous studies. An early Chinese study including 701 patients with COVID-19 showed that patients were more likely to develop AKI if their admission baseline SCR levels were higher (11.9 vs. 4%) (21). Data from a retrospective study of 306 patients from Sweden demonstrated that decreased baseline renal function increases the risk of developing AKI during hospitalization in COVID-19 patients. The risk ratios for experiencing AKI in patients with an eGFR between 30 and 59 ml/min and an eGFR <30 ml/min were 2.94 (95% CI: 1.17–7.34) and 9.93 (95% CI: 2.32–42.5), respectively (26). An international multicenter study of 939 patients identified that poor respiratory function (lower oxygen saturation and PaO2/FiO2 ratio) was a risk factor for the development of AKI (27). In addition, studies have shown that inflammatory indicators, such as C-reactive protein (27) and procalcitonin (28); underlying diseases, such as hypertension, diabetes, and chronic kidney disease; as well as coronary artery disease, are correlated with the occurrence of AKI (29, 30). There are also predictive models (scores or biomarkers) for AKI in COVID-19 patients that have been reported in previous studies. Gustavo et al. (31) investigated the capability of urinary kidney stress biomarkers (UKSB), including neutrophil gelatinase-associated lipocalin (NGAL) and tissue inhibitor of metalloproteinases-2 (TIMP-2) multiplied by insulin-like growth factor binding protein 7 (IGFBP7), for the early detection of AKI in 51 critically ill COVID-19 patients. The results showed that the AUCs of the ROC for NGAL and TIMP-2 × IGFBP7 predicting the occurrence of AKI during the entire hospitalization of patients were 0.706 (95% CI: 0.559–0.854) and 0.682 (95% CI: 0.535–0.829), respectively, with corresponding sensitivities and specificities of 54.5, 76.9, 40.0, and 88.4%. Naomi et al. (32) reported the application of serum biomarkers (SB), including serum NGAL and serum creatinine, for the prediction of AKI in 52 COVID-19 patients, with AUCs of 0.81 and 0.87, respectively. A prediction model for AKI based on proteinuria and hematuria yielded an AUC of 0.64 (95% CI: 0.62–0.67) in a large cohort study containing 5,980 COVID-19 patients; moreover, the predictive capability of the model was improved when creatinine and the presence of CKD were incorporated (33). In addition, studies have validated the predictive value of other indicators, such as D-dimer and albumin/creatinine ratio, for AKI in hospitalized COVID-19 patients (34). However, these predictive models (biomarkers) have some disadvantages. First and foremost, their performance has not been validated, which leads to a lack of confidence in their reproducibility and utility. Second, they focused only on a particular type

or class of indicators, which may present only a partial characterization of the patient's disease. Third, some models were constructed based on small sample sizes, such as the UKSB model and the SB model, which may not be representative of the whole cohort population. In contrast, in the present study, we screened indicators on the basis of seven dimensions of admission information for the construction of a predictive nomogram model of AKI during hospitalization based on a training set with 366 COVID-19 patients. Importantly, we verified the effectiveness of the nomogram in both training and validation cohorts and found that the nomogram displayed promising identification, goodness-of-fit, discriminative power, and clinical effectiveness.

We also investigated the predictive value of the model for patient prognosis. The mortality rate of patients in the high-risk group was higher than that of patients in the low-risk group; furthermore, the mortality rate of high-risk patients was greater than that of low-risk patients, with a hazard ratio of 1.98 for the training set and 2.10 for the validation set. This may be because high-risk patients are susceptible to the occurrence of AKI, while previous studies have demonstrated a higher mortality rate in COVID-19 patients with AKI (35). Regardless, the nomogram model could identify patients with a potentially poor prognosis at the beginning of their admission, which is helpful for the formulation of individualized treatment strategies and the arrangement of appropriate care and treatment at an early stage.

The study has several limitations. First, it is a public database-based study, and the results may have been influenced by confounding factors beyond our control. Second, although the model performed well in the validation set, we did not evaluate its performance in an independent external validation cohort. Third, the length of stay and last status of patients are influenced by other factors, especially treatment measures; therefore, relying on the model alone to predict prognosis is not sufficient. In addition, some other indicators, such as virus load or virus-related indicators, red blood cell count, and hemoglobin concentration, may have some correlation with the occurrence of AKI; however, we were unable to investigate these further due to the limitations of data availability, which may affect the reliability and stability of our conclusions. Moreover, due to the limitations of data availability, the difference in special treatment during hospitalization, such as hemodialysis technology, between high-risk and low-risk groups was not analyzed. Hence, the predictive capability for AKI and the prognostic value of the model needs to be verified in actual clinical practice.

Conclusion

We constructed a nomogram for the early prediction of AKI in hospitalized COVID-19 patients. The model demonstrated favorable performance on the basis of the AUCs of ROC, calibration curves, and decision curve analysis. Furthermore, the nomogram exhibited promising predictive values for a prognosis for the length of stay and last status of patients. The nomogram model is helpful to reasonably and effectively optimize the allocation and utilization of medical resources at an early stage to provide appropriate care and intervention management for patients, thereby improving prognosis and reducing mortality.

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 the Ethics Committee of Yantai Yuhuangding Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Methodology: CW, XL, and DW. Software: XC, SZ, and CW. Formal analysis: CW, HS, and XC. Resources: TJ and XL. Data curation: HS and SZ. Writing—original draft preparation: CW and HS. Writing—review and editing, supervision, and project administration: CL and TJ. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1047073/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Comparison of AUCs between Nomogram with SCR and BUN in the training set **(A)** and validation set **(B)**. Comparison of DCAs between Nomogram with SCR and BUN in the training set **(C)** and validation set **(D)**. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis; SCR, serum creatinine; BUN, blood urea nitrogen.

SUPPLEMENTARY TABLE 1
Comparison of characteristics between patients with AKI and non-AKI.

SUPPLEMENTARY TABLE 2
The parameters of the final multifactor model for AKI.

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Association between prothrombin time-international normalized ratio and prognosis of post-cardiac arrest patients: A retrospective cohort study

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Background: Cardiac arrest (CA) can activate blood coagulation. This study aimed to explore the potential prognostic value of prothrombin time–international normalized ratio (INR) in post-CA patients.

Methods: The clinical data of eligible subjects diagnosed with CA was extracted from the MIMIC-IV database as the training cohort. Restricted cubic spline (RCS), Kaplan–Meier (K-M) survival curve, and Cox regression analyses were conducted to elucidate the association between the INR and all-cause mortality of post-CA patients. Subgroup analysis, propensity score matching (PSM), and inverse probability of treatment (IPTW) were also conducted to improve stability and reliability. Data of the validation cohort were collected from the eICU database, and logistic-regression analyses were performed to verify the findings of the training cohort.

Results: A total of 1,324 subjects were included in the training cohort. A linear correlation existed between INR and the risk of all-cause death of post-CA patients, as shown in RCS analysis, with a hazard ratio (HR) >1 when INR exceeded 1.2. K-M survival curve preliminarily indicated that subjects with INR $\geq$ 1.2 presented lower survival rate and shorter survival time, and the high level of INR was independently associated with 30-day, 90-day, 1-year, and in-hospital mortalities, with multivariate-adjusted HR of 1.44 (1.20, 1.73), 1.46 (1.23, 1.74), 1.44 (1.23, 1.69), and 1.37 (1.14, 1.64), respectively. These findings were consistent and robust across the subgroup analysis, PSM and IPTW analyses, and validation cohort.

Conclusions: We systematically and comprehensively demonstrated that elevated INR was associated with increased short- and long-term all-cause mortality of post-CA patients. Therefore, elevated INR may be a promising biomarker with prognosis significance.

KEYWORDS

international normalized ratio, cardiac arrest, critical care, all-cause mortality, MIMIC-IV database

1. Introduction

Cardiac arrest (CA) is defined as the sudden cessation of cardiac ejection for various reasons. It has the characteristics of interrupted systemic circulation, respiratory arrest, and loss of consciousness (1). The incidence of CA is not uncommon, with approximately 140.7 out-of-hospital CA per 100,000 individuals in the United States, compared with 17.16 in-hospital CA per 1,000 hospitalizations (2). The treatment and care for CA patients have made considerable progress in recent years, but the prognosis of this group of patients remains poor, with an in-hospital survival rate of only 28.7% (3, 4). Clinicians need to deeply study the pathophysiological mechanism of the occurrence and progression of CA to search for new therapeutic targets. They also need to identify and determine some novel biomarkers related to the prognosis of post-CA patients to stratify high-risk patients promptly and take more effective therapeutic measures. All these endeavors can help improve the prognosis of patients (5).

Abnormity in the coagulation–fibrinolysis system is an important pathophysiological feature of post-CA patients (4, 6, 7). During CA and resuscitation, hypoxia and acidosis often occur. They can inflict vascular endothelial-cell damage, thereby stimulating tissue-factor release and thus initiating the exogenous-coagulation process. Besides, the excessively activated inflammatory response induced by the release of injury-related molecular patterns after tissue and cell damage can accelerate the activation of tissue-factor-dependent coagulation and also promote coagulation factor XII- and XI-dependent blood coagulation (8). Meanwhile, the endogenous fibrinolytic system is partially suppressed with decreased antithrombin, tissue-factor pathway inhibitor, protein C/S, and other anticoagulant substances (9). Coagulation and fibrinolysis-related indicators including activated partial thromboplastin time (APTT), fibrinogen degradation products, and D-dimer have been found to be closely related to the prognosis of post-CA patients and are expected to be promising biomarkers with prognosis significance (10–12).

As a sensitive and reliable indicator for screening and assessing exogenous-coagulation system disorders, the prothrombin time-international normalized ratio (INR) is extensively used to monitor anticoagulation therapy, assess liver dysfunction, and evaluate coagulation abnormalities such as DIC (13). A series of studies has also shown that elevated INR is closely associated with an adverse prognosis in various kinds of diseases, including trauma (14), sepsis (15), cerebral hemorrhage (16), and acute decompensated heart failure (17), with a promising application. However, the relationship between INR and the prognosis of post-CA patients remains unclear, particularly in long-term all-cause mortality. Accordingly, the present study aimed to illustrate the relationship between INR and short- and long-term all-cause mortalities in post-CA patients and thus identify a simple, objective, and reliable prognostic indicator. Our results can serve as a reference for the clinical management of post-CA patients.

2. Materials and methods

2.1. Data sources

The present research was a retrospective cohort study. All subjects' data were extracted from two large critical-care medical databases, which are free and open to researchers from all over the world. Data of the training cohort were collected from the Multiparameter Intelligent Monitoring in Intensive Care IV (MIMIC-IV; version 2.0) database (18, 19), which is jointly developed and run by the Massachusetts Institute of Technology (Cambridge, MA, USA) and the Beth Israel Deaconess Medical Center (BIDM, Boston, MA, USA). This database contains the detailed and comprehensive clinical data of about 250,000 patients admitted to the intensive care unit (ICU) and emergency unit of the Beth Israel Deaconess Medical Center from 2008 to 2019, including demography, laboratory tests, documented vital signs, medications administered, and so on. In-hospital and out-of-hospital death information is also available. The longest follow-up period for each patient was 1 year after their last discharge, providing great data support for clinical studies.

Data of the validation cohort were extracted from the eICU collaborative research database (20, 21), which is a multicenter database containing data of more than 200,000 ICU admissions across 208 United States hospitals between 2014 and 2015. Funded by the Philips eICU program, this database also includes vital signs, laboratory measurements, severity of illness, and diagnosis and treatment information. However, survival data and out-of-hospital follow-up information are unavailable.

2.2. Statement and authorization

The MIMIC-IV and eICU databases were de-identified, and patient identifiers were removed according to the Health Insurance Portability and Accountability Act Safe Harbor provision. The database was approved by ethical review boards, and requesting another ethical review for the present study was unnecessary. According to the database protocol, the author Tang passed the exam for "Protecting Human Research Participants" and gained access to the MIMIC-IV database (Record ID: 43449634). The reporting specifications for this study were in compliance with the STROBE statement.

2.3. Study population

Patients diagnosed with CA based on the International Classification of Diseases versions 9 and 10 diagnosis codes (ICD-9&10, "4,275," "I46," "I,462," "I,468," and "I,469") were included in this study. Further screening criteria for research subjects were as follows: (1) only the first admission for patients with multiple ICU admissions was considered; (2) adult patients were aged 18 years and above; (3) patients had an ICU stay of more than 24 h; (4) patients had a calculated survival time >0 (some organ-donation patients died earlier than the time of admission); (5) patients had no missing INR data within 24 h after ICU admission; and (6) patients were not treated with warfarin.

2.4. Research variable and outcomes

The independent variable was the INR of post-CA patients within 24 h after admission to ICU. The outcome events of interest were

all-cause death (in-hospital or within 30-day, 90-day, and 1-year after admission).

2.5. Data extraction and processing

Using PostgreSQL software (version 9.6, https://www.postgresql.org/), the author Tang extracted the clinical data of all subjects after obtaining authorization. These data included demographic characteristics, vital signs, laboratory tests, comorbidities, severity of illness scores, and treatments administered. Demographic characteristics included age, gender, and race. Vital signs included heart rate, respiratory rate, mean blood pressure (MBP), temperature, and pulse oxygen saturation. Laboratory tests included hemoglobin, white blood cells (WBCs), platelets, hematocrit, anion gap, bicarbonate, calcium, chloride, sodium, potassium, serum creatinine, blood urea nitrogen (BUN), glucose, alanine transaminase (ALT), bilirubin, INR, and APTT, which were collected within 24 h upon admission to ICU. Comorbidities [hypertension, diabetes mellitus, heart failure, atrial fibrillation, acute myocardial infarction (AMI), valvular heart disease (VHD), cardiomyopathy, pulmonary embolism, pulmonary hypertension, chronic obstructive pulmonary disease, renal diseases, liver diseases, stroke, and malignant tumor] were identified by corresponding ICD-9&10 codes, and the Charlson comorbidity index was calculated. The severity of ill scores was recorded for each subject, including the Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score II (SAPSII). Treatment measures such as mechanical ventilation, vasopressors, renal replacement therapy (RRT), transfusion of fresh frozen plasma (FFP) were also extracted. Variables with more than 20% missing values were not included in subsequent analyses. Variables with fewer missing data were filled with multiple imputation using the "mice" package of the R program.

2.6. Statistical analyses

Data of continuous variables were presented as the mean (standard deviations) for normal distributions or median (interquartile range) for skewed distributions, whereas categorical variables were expressed as numbers of cases and percentages. Two-group comparisons (survivor vs. nonsurvivor group, low INR vs. high-INR group) were conducted with student's *t*-test, Mann–Whitney U test, and χ^2 test (or Fisher's exact test) for normally distributed continuous, non-normally distributed continuous, and categorical variables, respectively.

Restricted cubic-spline analysis based on Cox proportional hazard model was performed to visualize the linear or nonlinear association between INR and all-cause mortality of post-CA patients, as well as to identify the inflection point as the cutoff to divide the whole cohort into low-INR and high-INR groups. Kaplan–Meier (K-M) survival curves were applied to visualize the cumulative probability of all-cause death across INR strata. Log-rank tests were used to compare the differences in risk between the groups.

Univariate and multivariate Cox proportional hazard models were conducted to assess the association between all-cause mortality and the two INR groups. They were presented as hazard ratios (HRs) and 95% confidence intervals (CI). No variables were adjusted in the univariate Cox regression analysis. The multivariate Cox model was adjusted with those variates whose effect on the independent variable exceeded 10% or clinically significant variables according to past experience, including age, gender, race, type of ICU for the first time, SOFA, SAPSII, Charlson comorbidity index, heart rate, MBP, anion gap, BUN, mechanical ventilation, vasopressors, RRT, aspirin, heparin, and the transfusion of FFP and platelets.

To further improve the reliability of the conclusion, the propensity score matching (PSM) and propensity score-based inverse probability of treatment (IPTW) were performed to balance the baseline characteristics of the two groups of subjects. In this study, nonparsimonious multivariable logistic-regression model was used to estimate the propensity score, and subjects in the low- and high-INR groups were matched one-to-one based on the propensity score by using the nearest neighbor matching algorithm with a caliper width of 0.25. For the IPTW analysis, a pseudo-population was generated using the estimated propensity scores as weights. The standardized mean difference was calculated to examine the efficiency of PSM and IPTW. For sensitivity analysis, K-M curves and Cox regression analysis were also reconducted on the PSM and IPTW cohorts to check the potential impact of INR on the all-cause mortality of patients with post-CA.

To evaluate the robustness of the findings of the present study, subgroup analysis was conducted to determine whether the association between INR and 1-year all-cause mortality of patients with post-CA was modified by age, gender, race, comorbidities, and disease severity. Sensitivity analyses were also performed in the post-CA patients with or without cardiac diseases (heart failure, AMI, cardiomyopathy, and VHD). The receiver operator characteristic (ROC) curve was drawn, and the area under the curve was calculated to compare the predictive performance of INR, SOFA, and SAPSII score in predicting the 1-year all-cause mortality of patients with post-CA.

The above statistical analyses were performed in R software (version 4.2.2) and EmpowerStats software (version 3.0, http://www.empowerstats.com/cn/, X&Y Solutions, Inc, Boston, MA, USA) for Windows system. $p < 0.05$ (two sided) was considered statistically significant.

3. Results

3.1. Clinical characteristics of subjects

The procedure of participant enrollment in this study is illustrated in Figure 1. A total of 1,324 eligible patients diagnosed with CA were ultimately included in the training cohort. In general, the median age of patients was 67.33 years old, of whom 821 were male and 503 were female. White ethnicity was the majority, with a total of 759, accounting for 57.33% of the whole cohort. At 1-year after admission, 502 patients (37.92%) survived and 822 patients (62.08%) died of various causes. Table 1 demonstrates the clinical characteristics of the survivors and nonsurvivors at 1-year follow-up. Compared with the survivor group, patients in the nonsurvivor presented a higher level of INR, APTT, WBCs, ALT, BUN, creatinine, and anion gap but lower hemoglobin, bicarbonate, calcium, and chloridion levels. In terms of vital signs, nonsurvival patients tended to have lower MBP, temperature, weight, and urine amount. However, their heart rates and respiratory rate increased significantly. Patients

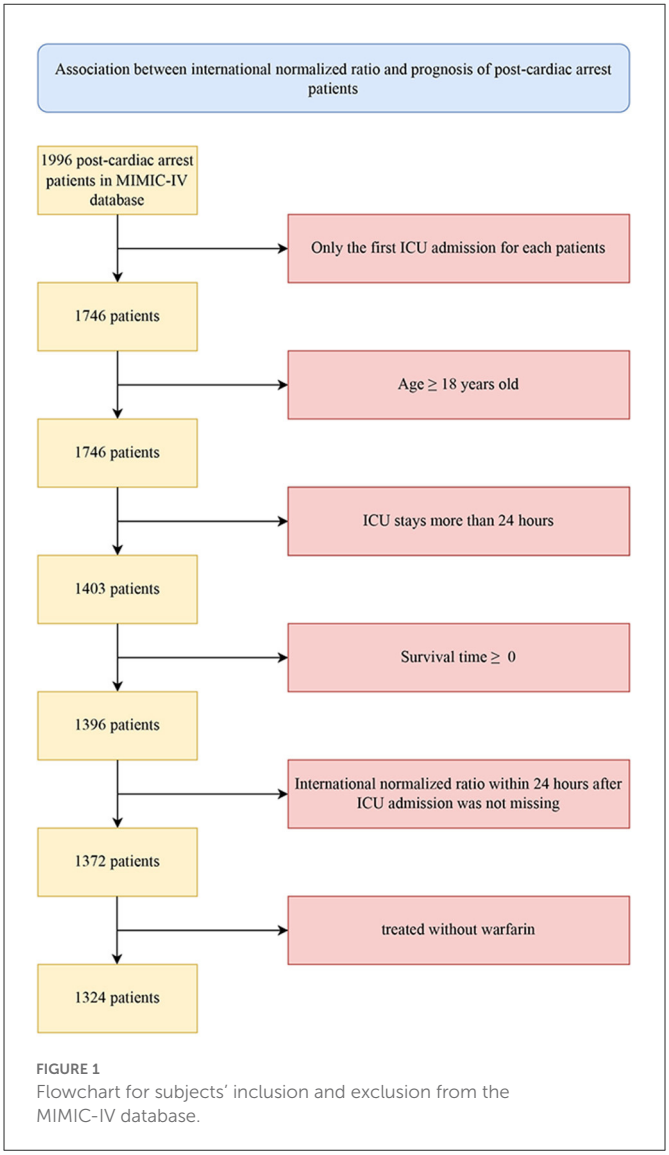

FIGURE 1
Flowchart for subjects' inclusion and exclusion from the MIMIC-IV database.

in the nonsurvivor tended to be more serious, with greater SOFA and SAPSII scores. They had higher incidence of comorbidities, including diabetes mellitus, renal and liver diseases, stroke, and malignant tumors. Besides, the use of mechanical ventilation, RRT, and vasopressor, as well as the transfusion of FFP, was also more common in the nonsurvivor than the survivor group, whereas the nonsurvivors were less likely to receive aspirin and heparin.

3.2. Associations between INR and all-cause mortality

Figure 2 shows the restricted cubic-spline model. A significant linear correlation existed between INR with all-cause mortality of post-CA patients, and the risk of death increased with elevated INR. Based on the result of restricted cubic-spline analysis, all subjects were divided into two groups according to the INR cutoff: low-INR group comprising 529 patients (INR $<$ 1.2), and high-INR group of 795 patients (INR $\geq$ 1.2). Consistently, K-M survival curves also illustrated that patients in the high-INR group were more likely to suffer from significantly elevated risks of all-cause death ($p <$ 0.001; Figures 3A–C). To confirm whether the elevated INR was an independent risk factor for the increase in all-cause mortality of post-CA patients, we further conducted univariate and multivariate Cox regression analyses (Figure 4). In the univariate model, INR was strongly associated with a significant increase in 30-day (unadjusted HR = 1.78; 95% CI = 1.51–2.10; Figure 4A), 90-day (adjusted HR = 1.82; 95% CI = 1.55–2.13; Figure 4B), 1-year (unadjusted HR = 1.82; 95% CI = 1.57–2.10; Figure 4C), and in-hospital (unadjusted HR = 1.48; 95% CI = 1.26–1.76; Figure 4D) all-cause mortalities. After multivariate adjustment for the various confounders, the positive relationship between INR and 30-day (adjusted HR = 1.44; 95% CI = 1.20–1.73; Figure 4A), 90-day (adjusted HR = 1.46; 95% CI = 1.23–1.74; Figure 4B), 1-year (adjusted HR = 1.44; 95% CI = 1.23–1.69; Figure 4C), and in-hospital (adjusted HR = 1.37; 95% CI = 1.14–1.64; Figure 4D) all-cause mortalities remained significant.

3.3. Outcomes after PSM and IPTW

To reduce the influence of confounding bias, the PSM and IPTW analyses were also performed in our studies. After PSM, 356 high-INR and 356 low-INR patients were enrolled in the final analysis. Almost all covariates were evenly distributed across the two groups, except for potassium and the transfusion of FFP (Table 2; Supplementary Figure 1). In the PSM cohort, the survival probability in the hospital and 30-day, 90-day, and 1-year after discharge of patients with post-CA was significantly higher in the low-INR than high-INR group (Figures 3D–F). The elevated INR still contributed to increased 30-day (HR = 1.33; 95% CI = 1.07–1.66), 90-day (HR = 1.37; 95% CI = 1.12–1.66), 1-year (HR = 1.33; 95% CI = 1.10–1.61), and in-hospital (HR = 1.30; 95% CI = 1.05–1.63) all-cause mortalities in the PSM analysis, as shown in Figure 4. After IPTW, no significant difference existed in baseline levels between the high-INR and low-INR groups (Supplementary Figure 1). The association of high INR level with excess all-cause mortality remained significant (Figure 4).

3.4. Subgroup analyses

Subgroup analysis of the association between INR and 1-year all-cause mortality was completed on the training cohort by using demographics, severity of illness scores, and several comorbidities, and results are presented in Table 3. Overall, the positive correlation between INR and all-cause mortality was generally consistent across subgroups, with higher INR associated with higher mortality. No significant interaction was observed in most strata (p = 0.0679–0.9719), except for AMI (p = 0.0434). Among post-CA patients, patients complicated with AMI tended to have higher risks of 1-year all-cause death for high INR than that of patients without AMI.

3.5. Sensitivity analyses and validation

Certain differences in clinical management existed across cardiogenic or non-cardiogenic post-CA patients, which may alter coagulation status and affect INR modification. Accordingly, we conducted sensitivity analyses to include only post-CA patients with

TABLE 1 Comparisons of the baseline characteristics between survivors and non-survivors at 1-year follow-up in the training cohort.

Variables	All	Survivors	Non-survivors	*p* value
N	1,324	502	822	
Age, years	67.33 (56.24–79.19)	64.22 (54.31–74.67)	69.64 (57.12–80.45)	<0.001
Male, %	821 (62.01%)	328 (65.34%)	493 (59.98%)	0.051
Race, %				0.027
White	759 (57.33%)	314 (62.55%)	445 (54.14%)	
Black	139 (10.50%)	48 (9.56%)	91 (11.07%)	
Asian	36 (2.72%)	12 (2.39%)	24 (2.92%)	
Other	390 (29.46%)	128 (25.50%)	262 (31.87%)	
First care unit				<0.001
CCU	532 (40.18%)	259 (51.59%)	273 (33.21%)	
MICU	474 (35.80%)	135 (26.89%)	339 (41.24%)	
Other	318 (24.02%)	108 (21.51%)	210 (25.55%)	
Vital signs				
HR, beats/minute	82.02 (70.80–95.29)	79.16 (69.23–90.33)	84.67 (72.52–98.00)	<0.001
RR, times/minute	19.90 (17.40–23.08)	19.18 (16.87–22.29)	20.50 (17.86–23.57)	<0.001
MBP, mmHg	77.28 (70.89–84.67)	78.49 (72.45–85.33)	76.61 (69.79–84.13)	0.003
Temperature, °C	36.72 (36.26–37.10)	36.78 (36.51–37.14)	36.66 (36.07–37.05)	<0.001
SpO2, %	97.82 (96.15–99.08)	97.83 (96.36–99.00)	97.82 (96.04–99.16)	0.734
Weight, kg	80.00 (67.00–95.40)	83.45 (70.05–99.25)	78.80 (65.02–92.67)	<0.001
Urine amount, L	1.26 (0.67–2.13)	1.59 (0.96–2.47)	1.09 (0.45–1.84)	<0.001
Laboratory tests				
Hemoglobin, g/dL	10.10 (8.40–12.20)	10.90 (9.00–12.78)	9.60 (8.03–11.60)	<0.001
Platelet, K/μl	163.00 (119.00–223.25)	162.50 (125.00–212.75)	163.50 (113.25–230.00)	0.843
WBC, K/μl	10.00 (7.10–13.60)	9.45 (7.00–12.90)	10.40 (7.10–14.20)	0.014
Hematocrit	30.90 (25.68–36.70)	32.90 (27.10–38.27)	29.90 (25.10–35.50)	<0.001
Anion gap, mmol/L	14.00 (12.00–16.00)	13.00 (11.00–15.00)	14.00 (12.00–17.00)	<0.001
Bicarbonate, mmol/L	19.00 (16.00–23.00)	20.50 (17.00–23.00)	18.00 (15.00–23.00)	<0.001
Calcium, mmol/L	7.90 (7.30–8.50)	8.05 (7.40–8.60)	7.90 (7.30–8.40)	0.004
Chloridion, mmol/L	102.00 (97.00–105.25)	103.00 (99.00–106.00)	101.00 (97.00–105.00)	0.001
Sodium, mmol/L	137.00 (134.00–140.00)	137.00 (135.00–139.00)	137.00 (133.00–140.00)	0.347
Potassium, mmol/L	3.80 (3.40–4.10)	3.80 (3.40–4.10)	3.70 (3.40–4.20)	0.929
Creatinine, mg/dl	1.10 (0.80–1.80)	0.90 (0.70–1.30)	1.30 (0.80–2.10)	<0.001
BUN, mg/dl	21.00 (14.00–35.00)	19.00 (13.00–30.00)	24.00 (15.00–41.00)	<0.001
Glucose, mg/dl	117.00 (96.00–146.00)	116.00 (97.25–137.75)	118.00 (96.00–150.00)	0.487
ALT	48.00 (23.75–126.25)	44.00 (24.00–96.00)	51.00 (23.00–151.75)	0.031
Bilirubin	0.50 (0.30–1.00)	0.50 (0.40–0.90)	0.50 (0.30–1.00)	0.864
INR	1.20 (1.10–1.40)	1.10 (1.00–1.30)	1.30 (1.10–1.50)	<0.001
APTT	29.50 (26.10–35.00)	28.20 (25.30–32.88)	30.60 (26.70–36.50)	<0.001
Scores				
SOFA	9.00 (5.00–12.00)	7.00 (4.00–11.00)	10.00 (6.00–13.00)	<0.001
SAPSII	45.00 (35.00–57.00)	39.00 (30.00–50.00)	49.00 (40.00–61.00)	<0.001
Charlson index	6.00 (4.00–8.00)	5.00 (4.00–7.00)	7.00 (5.00–9.00)	<0.001

(Continued)

TABLE 1 (Continued)

Variables	All	Survivors	Non-survivors	*p* value
Comorbidities, n (%)				
Hypertension	522 (39.43%)	231 (46.02%)	291 (35.40%)	<0.001
Diabetes mellitus	470 (35.50%)	149 (29.68%)	321 (39.05%)	<0.001
Heart failure	513 (38.75%)	194 (38.65%)	319 (38.81%)	0.953
Atrial fibrillation	455 (34.37%)	242 (34.52%)	247 (36.81%)	0.376
AMI	398 (30.06%)	151 (30.08%)	247 (30.05%)	0.990
VHD	15 (1.13%)	8 (1.59%)	7 (0.85%)	0.216
Cardiomyopathy	85 (6.42%)	37 (7.37%)	48 (5.84%)	0.270
Pulmonary embolism	60 (4.53%)	23 (4.58%)	37 (4.50%)	0.946
Pulmonary hypertension	49 (3.70%)	14 (2.79%)	35 (4.26%)	0.170
COPD	357 (26.96%)	137 (27.29%)	220 (26.76%)	0.834
Renal diseases	385 (29.08%)	110 (21.91%)	275 (33.45%)	<0.001
Liver diseases	224 (16.92%)	69 (13.75%)	155 (18.86%)	0.016
Stroke	111 (8.38%)	27 (5.38%)	84 (10.22%)	0.002
Malignancy	163 (12.31%)	30 (5.98%)	133 (16.18%)	<0.001
Therapies, n (%)				
Mechanical ventilation	1,223 (92.37%)	450 (89.64%)	773 (94.04%)	0.003
RRT	85 (6.42%)	18 (3.59%)	67 (8.15%)	0.001
Vasopressor	828 (62.54%)	287 (57.17%)	541 (65.82%)	0.002
PCI	68 (5.14%)	33 (6.57%)	35 (4.26%)	0.064
Therapies, n (%)				
Assisted circulation	20 (1.51%)	9 (1.79%)	11 (1.34%)	0.511
ECMO	22 (1.66%)	8 (1.59%)	14 (1.70%)	0.880
Aspirin	596 (45.02%)	255 (50.80%)	341 (41.48%)	<0.001
Heparin	943 (71.22%)	384 (76.49%)	559 (68.00%)	<0.001
Transfusion of FFP	132 (9.97%)	38 (7.57%)	94 (11.44%)	0.023
Transfusion of platelet	85 (6.42%)	25 (4.98%)	60 (7.30%)	0.095

CCU, cardiac care unit; MICU, medical intensive care unit; HR, heart rate; RR, respiratory rate; MBP, mean blood pressure; WBC, white blood cell; BUN, blood urea nitrogen; ALT, alanine transaminase; INR, international normalized ratio; APTT, activated partial thromboplastin time; SOFA, the sequential organ failure assessment; SAPSII, the simplified acute physiology score II; AMI, acute myocardial infarction; VHD, valvular heart disease; COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; PCI, percutaneous coronary intervention; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma.

cardiac diseases or ones without cardiac diseases, respectively. Similar to main analyses, INR was still a significant and robust predictor for 1-year all-cause mortality of post-CA patients with or without cardiac diseases (Table 4).

We then performed an external validation in the validation cohort from the eICU database, and the baseline characteristics of subjects are presented in Supplementary Table 1. In the crude model without adjusting for covariates, high INR was related to the elevated in-hospital mortality (unadjusted OR = 2.07; 95% CI = 1.63–2.64; Table 5). In model I after adjusting for age, gender, and race, high INR was also associated with increased in-hospital mortality (adjusted OR = 2.03; 95% CI = 1.59–2.60; Table 5). Model II further adjusted for other confounders, including the type of ICU for the first time, APACHE-IV scores, heart rate, MBP, anion gap, BUN, the use of mechanical ventilation and RRT, the admission of vasopressors, aspirin, and heparin, and the transfusion of FFP and platelets. Elevated INR still can independently predict the high in-hospital mortality (adjusted OR = 1.34; 95% CI = 1.01–1.78; Table 5).

3.6. Predictive values of INR and some severity scores for 1-year all-cause mortality

ROC curves were obtained to evaluate the predictive performance of INR and some severity scoring systems (SOFA and SAPSII) for 1-year all-cause mortality, as shown in Figure 5. Compared with SAPSII score (area under ROC = 0.684; 95% CI: 0.654–0.714), the INR (area under ROC = 0.647, 95% CI: 0.617–0.677) had the slightly worse power for predicting the 1-year all-cause mortality of patients with post-CA, whereas the performance was comparable with SOFA score

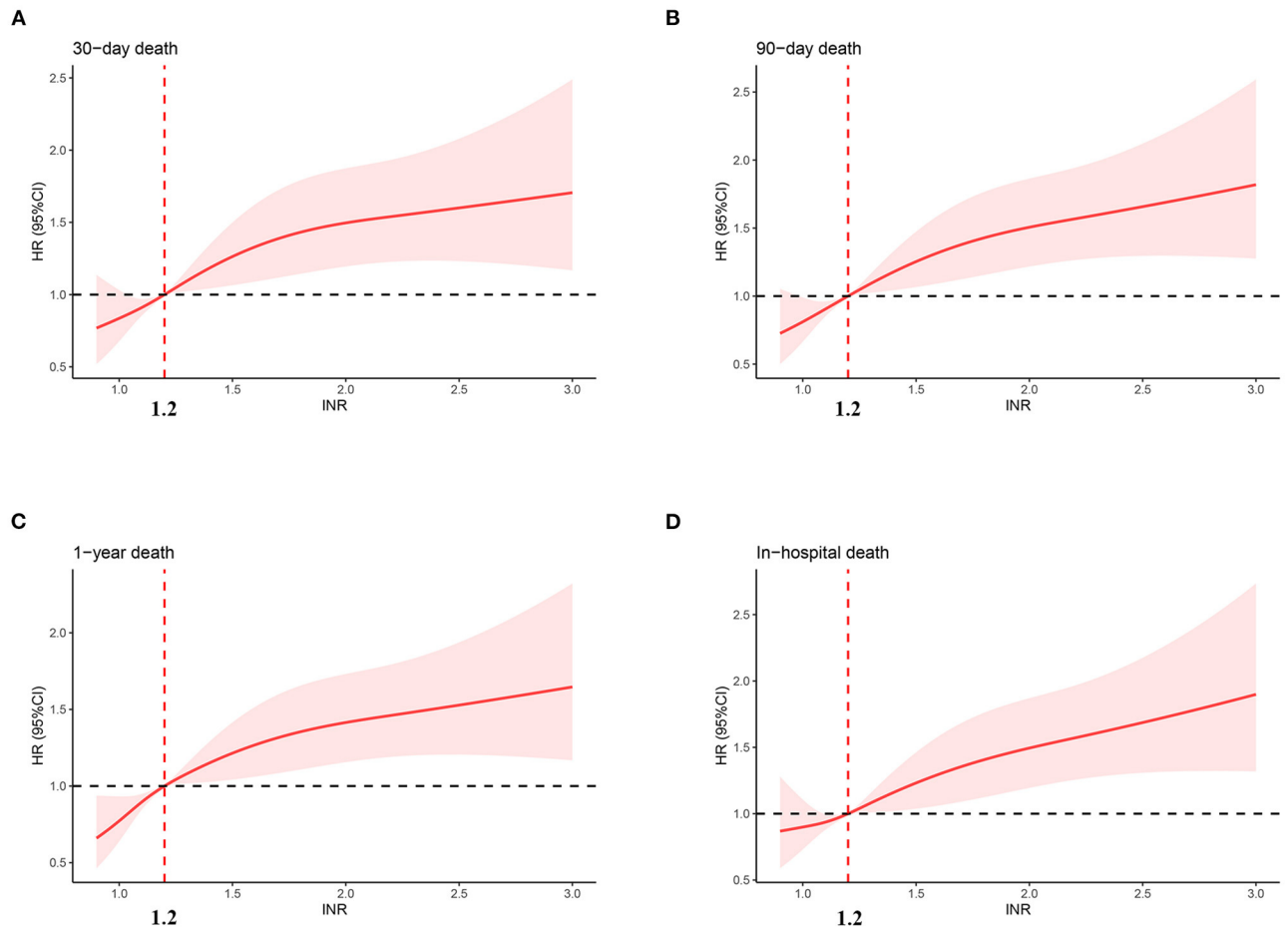

FIGURE 2
Association between INR and hazard ratio of 30-day **(A)**, 90-day **(B)**, 1-year **(C)**, and in-hospital **(D)** all-cause death. INR, international normalized ratio.

(area under ROC = 0.632; 95% CI = 0.601–0.663). Besides, compared with SOFA and SASPII scores, INR displayed a relatively higher specificity (71.3%) but lower sensitivity (51.5%) for predicting 1-year all-cause mortality in post-CA patients with 1.2 as the cutoff point (Supplementary Table 2).

4. Discussion

The clinical data of MIMIC-IV and eICU databases were analyzed retrospectively to evaluate the possibility of INR predicting the prognosis of post-CA patients. Results showed that the INR within 24 h after admission to ICU was an independent risk factor for 30-day, 90-day, 1-year, and in-hospital all-cause mortalities of post-CA patients. First, we explored the potential relationship between INR and all-cause mortality by restricted cubic-spline analysis. A significant linear positive correlation was found between INR and all-cause mortality, and the risk of all-cause death increased significantly when INR was <1.2 (HR > 1). K-M survival curve and Cox regression analysis further confirmed that the all-cause mortality in patients with high INR was significantly higher than that in patients with low INR, which was still robust in the subgroup analyses, PSM and IPTW analyses, and validation cohort. Overall, this study illustrated that INR was helpful for the risk stratification of post-CA patients to identify high-risk ones and contribute to the clinical management of patients.

Several studies have demonstrated that a high level of INR is strongly associated with poor prognosis in various diseases. Zheng et al. (22) illustrated that INR is positively correlated with all-cause mortality in patients with sepsis, with an adjusted odds ratio (OR) of 1.86 (95% CI: 1.37–2.52) for in-hospital mortality, and an adjusted HR of 1.47 (95% CI: 1.24–1.74) for 1-year mortality. Among patients with coronary artery disease, an increased risk of all-cause mortality has been found in those with high levels of INR (INR > 1.06) during a median follow-up of 5.25 years (23). Ki-Hong et al. (24) also reported that prothrombin time–INR prolongation was associated with poor in-hospital survival (adjusted OR = 0.28; 95% CI = 0.11–0.69) in adult out-of-hospital CA with cardiac etiology. In this multicenter cross-sectional study, only the relation between INR and survival at discharge is analyzed. The survival time of subjects, which is significant for evaluating the condition and severity of patients, is not considered. The association between INR and long-term prognosis of post-CA patients is also not explored due to the lack of follow-up after discharge. In the present study, we systematically and comprehensively analyzed the relationship of high level of INR with the short-term (30-day, 90-day, and in-hospital mortalities) and long-term (1-year mortality)

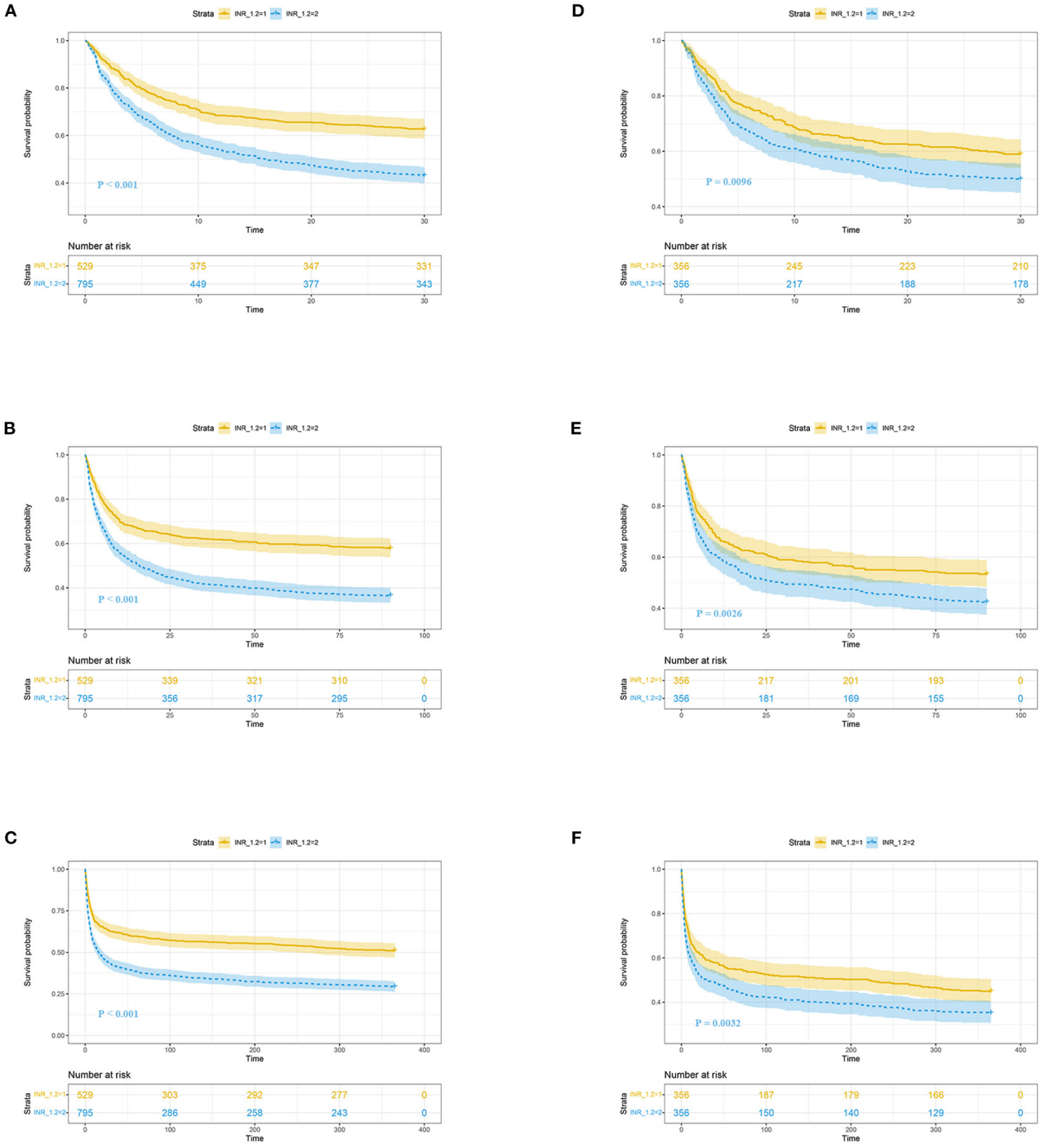

FIGURE 3
K-M survival curves of post-CA patients with high (blue, INR ≥ 1.2) and low (yellow, INR < 1.2) INR at 30-day **(A, D)**, 90-day **(B, E)**, and 1-year **(C, F)** follow-up. **(A–F)** Reflect the results before and after propensity score matching, respectively. CA, cardiac arrest; INR, international normalized ratio.

outcome of post-CA patients, considering the occurrence of outcome events and the occurrence time of events. The baseline data we collected were also more comprehensive and complete, including demographic data, vital signs, laboratory tests, disease-severity scores, treatment measures, etc. They were adjusted by multivariate Cox regression analysis, PSM and IPTW analyses, and other statistical methods, which were conducive to enhancing the reliability of our results.

As a prognostic biomarker, INR may have the following advantages. First, INR is calculated according to the prothrombin time and the international sensitivity index of the assay reagent. Compared with prothrombin time, INR presents better consistency across different medical institutions, and the measurement results are comparable (25). Second, INR can be detected readily and quickly in most hospitals, with the strengths of timeliness and low cost (26). Last, coagulation disorders in CA patients are being commonly

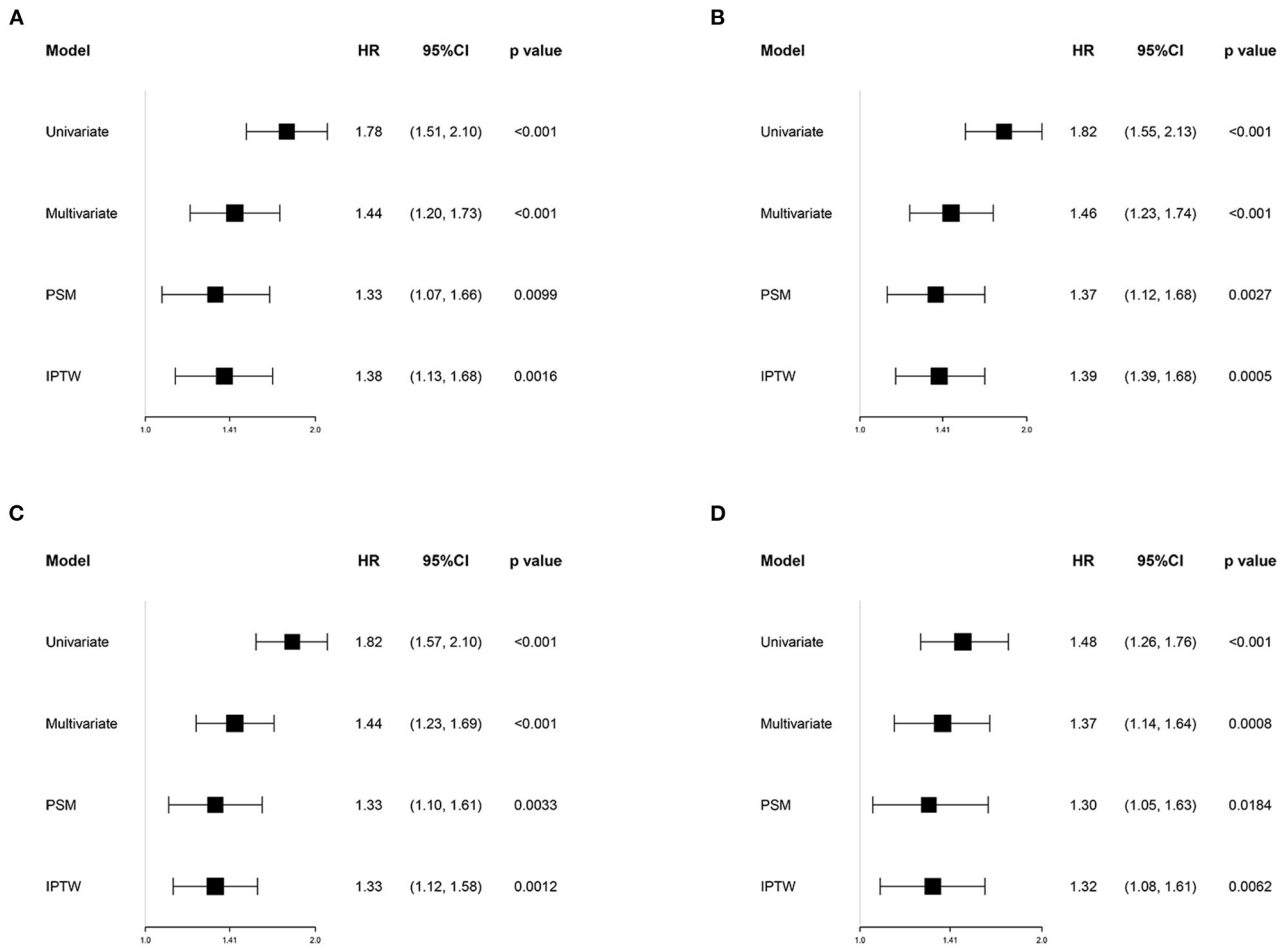

FIGURE 4
Association between INR group and 30-day **(A)**, 90-day **(B)**, 1-year **(C)**, and in-hospital **(D)** all-cause mortalities in different models. Univariate model was adjusted for none. Multivariate model was adjusted for age, gender, race, type of ICU for the first time, SOFA, SAPSII, Charlson comorbidity index, heart rate, mean blood pressure, anion gap, serum urea nitrogen, mechanical ventilation, vasopressors, renal replacement therapy, aspirin, warfarin, heparin, and the transfusion of fresh frozen plasma and platelets. HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SOFA, the sequential organ failure assessment; SAPSII, the simplified acute physiology score II.

recognized, especially abnormalities in exogenous coagulation pathways triggered by tissue factors (27). As a commonly used laboratory indicator reflecting changes in exogenous coagulation pathways, a certain theoretical basis exists for INR to predict the prognosis of post-CA patients.

The pathophysiological mechanism by which elevated INR is associated with poor prognosis in post-CA patients is unclear, but multiple possibilities could explain the increased INR in post-CA patients. First, the consumption of coagulation factors can lead to increased INR after the excessive activation of the coagulation system. Direct damages to cells and tissues during the no blood flow and perfusion period after CA, ischemia–reperfusion injury after spontaneous circulation recovery, and overactive neurohormones can all induce endothelial-cell dysfunction and trigger the expression of tissue factors. These phenomena can generate thrombin and cause coagulation by a series of cascade reaction (28). Moreover, some well-known platelet activators such as hypoxia, ischemia, thrombin, catecholamines, etc. can be induced after CA, thereby contributing to platelet hyperactivation and leading to a thrombo-inflammatory state characterized by the expression of tissue factors and thrombin produce (9). Tissue factor-mediated coagulation activation and platelet activation are also the main triggers of DIC, which are characterized by systemic-coagulation activation and insufficient endogenous fibrinolysis, leading to intravascular fibrin formation and microvascular thrombosis (29). The prevalence of overt DIC in post-CA patients is not low, about 42–54%, and a higher DIC score is closely related to increase in-hospital mortality in patients with out-of-hospital CA (OR = 1.89; 95% CI = 1.48–2.41) (30). Prolonged prothrombin time and increased INR are fairly common in liver dysfunction, and another possible explanation for increased INR is hypoxic liver injury after CA. Due to the loss of blood supply, multiple tissues and organs including the liver suffer from severe ischemia and hypoxia after CA, resulting in centrilobular liver cell necrosis and acute liver injury. Furthermore, reperfusion injury after the recovery of spontaneous circulation due to timely cardiopulmonary resuscitation is an important cause of liver injury (31). According to Roedl et al. (32), the prevalence of hypoxic liver injury in out-of-hospital and in-hospital CA patients have similar values of 21 and 19%, respectively. The occurrence of hypoxic liver injury can predict the possible terrible outcome of post-CA patients. Compared

TABLE 2 The baseline characteristics of post-CA patients grouped by INR before and after PSM.

Variables	Before PSM			After PSM		
	INR < 1.2	INR ≥ 1.2	SMD	INR < 1.2	INR ≥ 1.2	SMD
N	529	795		356	356	
Age, years	65.45 (54.34–76.23)	69.16 (56.94–80.38)	0.192	67.56 (58.36–78.77)	69.38 (55.72–80.37)	0.013
Male, %	309 (58.41%)	512 (64.40%)	0.123	210 (58.99%)	197 (55.34%)	0.074
Race, %			0.220			0.083
White	291 (55.01%)	468 (58.87%)		201 (56.46%)	191 (53.65%)	
Black	41 (7.75%)	98 (12.33%)		32 (8.99%)	40 (11.24%)	
Asian	14 (2.65%)	22 (2.77%)		12 (3.37%)	11 (3.09%)	
Other	183 (34.59%)	207 (26.04%)		111 (31.18%)	114 (32.02%)	
First care unit			0.169			0.011
CCU	231 (43.67%)	301 (37.86%)		153 (42.98%)	151 (42.42%)	
MICU	164 (31.00%)	310 (38.99%)		112 (31.46%)	113 (31.74%)	
Other	134 (25.33%)	184 (23.14%)		91 (25.56%)	92 (25.84%)	
Vital signs						
HR, beats/minute	78.52 (66.79–91.69)	84.22 (73.84–98.21)	0.371	80.61 (69.16–92.94)	79.83 (70.86–91.05)	0.002
RR, times/minute	19.60 (17.30–22.77)	20.12 (17.55–23.25)	0.102	19.66 (17.39–23.19)	19.60 (17.27–22.59)	0.032
MBP, mmHg	78.84 (73.28–87.00)	75.91 (69.33–82.71)	0.355	77.98 (72.20–85.29)	79.11 (72.49–85.50)	0.039
Temperature, °C	36.74 (36.33–37.08)	36.71 (36.24–37.11)	0.054	36.77 (36.39–37.09)	36.73 (36.32–37.15)	0.008
SpO2, %	98.00 (96.39–99.15)	97.67 (95.98–98.99)	0.189	97.82 (96.22–99.01)	98.00 (96.37–99.15)	0.027
Weight, kg	80.00 (67.90–94.30)	80.00 (66.60–96.15)	0.016	79.00 (66.20–94.00)	79.00 (64.47–95.53)	0.047
Urine amount, L	1.50 (0.90–2.37)	1.14 (0.52–1.90)	0.232	1.33 (0.81–2.18)	1.29 (0.81–2.06)	0.020
Laboratory tests						
Hemoglobin, g/dL	11.20 (9.10–13.00)	9.40 (8.00–11.20)	0.558	10.40 (8.60–12.40)	10.35 (8.80–12.00)	0.021
Platelet, K/μl	171.00 (134.00–225.00)	157.00 (108.00–223.00)	0.116	171.00 (126.00–231.25)	167.50 (124.00–223.00)	0.023
WBC, K/μl	9.80 (7.00–13.10)	10.10 (7.10–14.00)	0.133	10.05 (6.90–13.62)	9.95 (7.20–13.20)	<0.001
Hematocrit	33.80 (27.80–38.70)	29.20 (24.90–34.30)	0.496	31.55 (26.00–37.02)	31.35 (27.02–36.23)	0.018
Laboratory tests						
Anion gap, mmol/L	13.00 (11.00–15.00)	14.00 (12.00–17.00)	0.324	13.00 (11.00–16.00)	13.00 (11.00–16.00)	0.003
Bicarbonate, mmol/L	20.00 (16.00–23.00)	19.00 (15.00–23.00)	0.164	19.00 (16.00–23.00)	19.00 (16.00–23.00)	0.020
Calcium, mmol/L	8.00 (7.40–8.50)	7.90 (7.30–8.40)	0.120	8.00 (7.40–8.50)	8.00 (7.40–8.50)	0.015
Chloridion, mmol/L	102.00 (98.00–105.00)	102.00 (97.00–106.00)	0.121	102.00 (97.75–106.00)	102.00 (98.00–106.00)	0.011
Sodium, mmol/L	137.00 (135.00–140.00)	137.00 (133.00–140.00)	0.096	137.00 (134.00–139.00)	137.00 (134.00–140.00)	0.048
Potassium, mmol/L	3.70 (3.30–4.10)	3.80 (3.40–4.20)	0.238	3.80 (3.40–4.12)	3.70 (3.40–4.00)	0.103
Creatinine, mg/dl	0.90 (0.70–1.40)	1.30 (0.85–2.10)	0.325	1.00 (0.70–1.60)	1.05 (0.70–1.52)	0.005
BUN, mg/dl	17.00 (12.00–26.00)	24.00 (15.00–41.00)	0.487	19.00 (14.00–29.00)	20.00 (14.00–30.00)	0.011
Glucose, mg/dl	119.00 (101.00–144.00)	116.00 (95.00–147.00)	0.001	121.00 (101.75–148.00)	116.00 (96.00–145.00)	0.011
ALT	57.00 (27.00–138.00)	42.00 (22.00–119.00)	0.179	51.00 (24.00–137.00)	42.00 (22.00–95.50)	0.026
Bilirubin	0.40 (0.30–0.70)	0.60 (0.40–1.20)	0.350	0.50 (0.30–0.80)	0.50 (0.30–0.80)	0.043
APTT	27.30 (24.52–30.20)	31.90 (27.70–38.10)	0.545	28.20 (25.50–31.50)	29.25 (25.90–33.50)	0.040
Charlson index	5.00 (3.00–7.00)	7.00 (5.00–9.00)	0.468	6.00 (4.00–8.00)	6.00 (4.00–8.00)	0.017
Comorbidities, n (%)						
Hypertension	247 (46.69%)	275 (34.59%)	0.248	157 (44.10%)	159 (44.66%)	0.011

(Continued)

TABLE 2 (Continued)

Variables	Before PSM			After PSM		
	INR < 1.2	INR ≥ 1.2	SMD	INR < 1.2	INR ≥ 1.2	SMD
Diabetes mellitus	165 (31.19%)	305 (38.36%)	0.151	130 (36.52%)	126 (35.39%)	0.023
Heart failure	175 (33.08%)	338 (42.52%)	0.195	130 (36.52%)	141 (39.61%)	0.064
Atrial fibrillation	134 (25.33%)	321 (40.38%)	0.325	116 (32.58%)	119 (33.43%)	0.018
AMI	168 (31.76%)	230 (28.93%)	0.062	110 (30.90%)	105 (29.49%)	0.031
VHD	5 (0.95%)	10 (1.26%)	0.030	5 (1.40%)	6 (1.69%)	0.023
Cardiomyopathy	28 (5.29%)	57 (7.17%)	0.078	19 (5.34%)	19 (5.34%)	<0.001
Pulmonary embolism	16 (3.02%)	44 (5.53%)	0.124	13 (3.65%)	12 (3.37%)	0.015
Pulmonary hypertension	8 (1.51%)	41 (5.16%)	0.204	8 (2.25%)	13 (3.65%)	0.083
COPD	141 (26.65%)	216 (27.17%)	0.012	112 (31.46%)	104 (29.21%)	0.049
Renal diseases	104 (19.66%)	281 (35.35%)	0.357	93 (26.12%)	85 (23.88%)	0.052
Comorbidities, n (%)						
Liver diseases	42 (7.94%)	182 (22.89%)	0.423	36 (10.11%)	30 (8.43%)	0.058
Stroke	45 (8.51%)	66 (8.30%)	0.007	34 (9.55%)	30 (8.43%)	0.039
Malignancy	43 (8.13%)	120 (15.09%)	0.219	37 (10.39%)	35 (9.83%)	0.019
Therapies, n (%)						
Mechanical ventilation	479 (90.55%)	744 (93.58%)	0.113	330 (92.70%)	336 (94.38%)	0.069
RRT	24 (4.54%)	61 (7.67%)	0.131	20 (5.62%)	20 (5.62%)	<0.001
Vasopressor	292 (55.20%)	536 (67.42%)	0.253	223 (62.64%)	224 (62.92%)	0.006
PCI	40 (7.56%)	28 (3.52%)	0.177	18 (5.06%)	20 (5.62%)	0.025
Assisted circulation	8 (1.51%)	12 (1.51%)	<0.001	8 (2.25%)	5 (1.40%)	0.063
ECMO	5 (0.95%)	17 (2.14%)	0.097	5 (1.40%)	5 (1.40%)	<0.001
Aspirin	246 (46.50%)	350 (44.03%)	0.050	170 (47.75%)	165 (46.35%)	0.028
Heparin	413 (78.07%)	530 (66.67%)	0.257	260 (73.03%)	257 (72.19%)	0.019
Therapies, n (%)						
Transfusion of FFP	21 (3.97%)	111 (13.96%)	0.355	21 (5.90%)	31 (8.71%)	0.108
Transfusion of platelet	17 (3.21%)	68 (8.55%)	0.228	16 (4.49%)	23 (6.46%)	0.086
Scores						
SOFA	8.00 (4.00–11.00)	10.00 (6.00–13.00)	0.448	9.00 (5.00–12.00)	8.00 (5.00–12.00)	0.003
SAPSII	41.00 (31.00–52.00)	48.00 (38.00–60.00)	0.461	45.50 (35.00–55.00)	43.00 (36.00–55.25)	0.010

PSM, propensity score matching; CCU, cardiac care unit; MICU, medical intensive care unit; HR, heart rate; RR, respiratory rate; MBP, mean blood pressure; WBC, white blood cell; BUN, blood urea nitrogen; ALT, alanine transaminase; INR, international normalized ratio; APTT, activated partial thromboplastin time; SOFA, the sequential organ failure assessment; SAPSII, the simplified acute physiology score II; AMI, acute myocardial infarction; VHD, valvular heart disease; COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; PCI, percutaneous coronary intervention; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma.

with those without hypoxic liver injury, the 1-year mortality of post-CA patients complicated with hypoxic liver injury is significantly higher (61 vs. 49%, $p < 0.001$).

Herein, subgroup analysis was conducted for sensitivity analysis to improve the robustness of our research results. In all subgroups stratified by age, gender, race, comorbidities, and disease-severity scores, the association of high-level INR with increased 1-year all-cause mortality of post-CA patients was a consistent finding. The conclusion that INR was positively associated with mortality still stood in post-CA patients accompanied with stroke, pulmonary embolism, or VHD, but it was not statistically significant, which may be attributed to the limited sample size after stratification. We also found that INR interacted with AMI on the 1-year all-cause death in post-CA patients (p for interaction < 0.05). In post-CA patients with AM, the relationship between INR ≥ 1.2 and the increase in all-cause mortality was more significant. One possible explanation was that AMI can promote inflammatory response and neurohormone activation, which were previously considered as important triggers leading to the activation of coagulation system, consumption of coagulation factors, and increase in INR (17).

A series of disease severity scoring systems, such as SOFA and SAPSII scores, have been developed and applied satisfactorily to assess the severity of critically ill patients and predict their prognosis, including the outcome of post-CA patients. Matsuda et al. (33) found

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TABLE 3 Subgroup analysis of the association between INR and 1-year all-cause mortality.

Variables	N	INR		*p* for interaction
		<1.2	≥1.2	
Gender				0.4065
Female	503	1 (ref)	1.70 (1.36, 2.13)	
Male	821	1 (ref)	1.94 (1.59, 2.36)	
Age				0.9790
< 65	589	1 (ref)	1.75 (1.39, 2.20)	
≥ 65	735	1 (ref)	1.81 (1.49, 2.19)	
Race				0.5606
White	759	1 (ref)	1.92 (1.56, 2.36)	
Black	139	1 (ref)	2.59 (1.54, 4.35)	
Asian	36	1 (ref)	1.47 (0.63, 3.45)	
Other	390	1 (ref)	1.65 (1.28, 2.11)	
Hypertension				0.2826
No	802	1 (ref)	1.94 (1.60, 2.35)	
Yes	522	1 (ref)	1.58 (1.25, 2.00)	
Diabetes				0.2281
No	854	1 (ref)	1.65 (1.37, 1.99)	
Yes	470	1 (ref)	2.13 (1.66, 2.74)	
AMI				0.0434
No	926	1 (ref)	1.63 (1.37, 1.94)	
Yes	398	1 (ref)	2.33 (1.78, 3.06)	
Atrial fibrillation				0.4783
No	869	1 (ref)	1.85 (1.54, 2.21)	
Yes	455	1 (ref)	1.73 (1.33, 2.26)	
VHD				0.1978
No	1,309	1 (ref)	1.83 (1.58, 2.13)	
Yes	15	1 (ref)	1.01 (0.38, 5.41)	
Pulmonary hypertension				0.0679
No	1,275	1 (ref)	1.77 (1.52, 2.06)	
Yes	49	1 (ref)	5.67 (1.35, 23.73)	
Pulmonary embolism				0.0769
No	1,264	1 (ref)	1.87 (1.61, 2.17)	
Yes	60	1 (ref)	1.03 (0.66, 1.88)	
Heart failure				0.1236
No	811	1 (ref)	1.65 (1.38, 1.98)	
Yes	513	1 (ref)	2.28 (1.76, 2.95)	
COPD				0.5496
No	967	1 (ref)	1.76 (1.48, 2.09)	
Yes	357	1 (ref)	1.97 (1.48, 2.63)	
Renal diseases				0.8506
No	939	1 (ref)	1.73 (1.45, 2.06)	
Yes	385	1 (ref)	1.94 (1.45, 2.60)	

(Continued)

TABLE 3 (Continued)

Variables	N	INR		p for interaction
		<1.2	≥1.2	
Liver diseases				0.1442
No	1,100	1 (ref)	1.72 (1.47, 2.02)	
Yes	224	1 (ref)	2.56 (1.56, 4.19)	
Cardiomyopathy				0.5052
No	1,239	1 (ref)	1.80 (1.55, 2.09)	
Yes	85	1 (ref)	2.35 (1.17, 4.72)	
Stroke				0.1069
No	1,213	1 (ref)	1.88 (1.60, 2.19)	
Yes	111	1 (ref)	1.30 (0.83, 2.02)	
Malignancy				0.7688
No	1,161	1 (ref)	1.75 (1.49, 2.05)	
Yes	163	1 (ref)	2.01 (1.33, 3.04)	
SOFA				0.3772
<5	262	1 (ref)	1.47 (1.01, 2.14)	
≥5	1,062	1 (ref)	1.76 (1.50, 2.07)	
SAPSII				0.9719
<40	469	1 (ref)	1.63 (1.24, 2.15)	
≥40	855	1 (ref)	1.64 (1.38, 1.96)	

INR, international normalized ratio; AMI, acute myocardial infarction; VHD, valvular heart disease; COPD, chronic obstructive pulmonary disease; SOFA, the sequential organ failure assessment; SAPSII, the simplified acute physiology score II.

TABLE 4 Sensitivity analysis of the association between INR and 1-year all-cause mortality in post-CA patients with or without cardiac diseases.

	N	Crude		Model I		Model II	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Without cardiac diseases							
INR group	627						
<1.2	257	1 (ref)		1(ref)		1(ref)	
≥1.2	370	1.50 (1.22, 1.84)	<0.001	1.57 (1.28, 1.93)	<0.001	1.27 (1.01, 1.60)	0.0395
With cardiac diseases							
INR group	697						
<1.2	272	1 (ref)		1 (ref)		1 (ref)	
≥1.2	425	2.23 (1.80, 2.77)	<0.001	2.14 (1.72, 2.66)	<0.001	1.63 (1.29, 2.06)	<0.001

Crude model was adjusted for none. Model I was adjusted for age, gender, and race. Model II was adjusted for age, gender, race, type of intensive care unit for the first time, SOFA, SAPSII, Charlson comorbidity index, heart rate, mean arterial pressure, anion gap, blood urea nitrogen, mechanical ventilation, vasopressors, renal replacement therapy, aspirin, heparin, and the transfusion of fresh frozen plasma and platelets.
CA, cardiac arrest; HR, hazard ratio; INR, international normalized ratio; SOFA, the sequential organ failure assessment; SAPSII, the simplified acute physiology score II.

that patients with post-CA syndrome who survive or have favorable neurological outcome tend to have a lower SOFA score, and SOFA score at admission is an independent predictor of 30-day survival (OR = 0.68; 95% CI = 0.59–0.78). To evaluate the predictive efficiency of INR for the prognosis of post-CA patients, the present study also performed ROC analysis and calculated the area under the curve to compare the performance of INR with SOFA and SAPSII scores in predicting the 1-year all-cause mortality. Overall, the performance of INR was roughly equal to SOFA score but slightly inferior to SAPSII score. However, in clinical practice, acquiring complete and systemic SOFA or SAPSII scores in a timely manner is often difficult. SOFA score (34) becomes available only after the collection of oxygenation index, platelet count, serum bilirubin concentration, serum creatinine concentration, urine volume, Glasgow score, and cardiovascular function. SAPSII score (35) also requires the data of vital signs (e.g., heart rate and systolic blood pressure) and of laboratory tests (e.g., serum sodium and potassium), thereby limiting the clinical convenience and timeliness of these scores to some extent.

TABLE 5 The logistics regression analyses of INR for predicting 1-year all-cause mortality of post-CA patients in validation cohort.

	Crude		Model I		Model II	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
INR	1.39 (1.25, 1.56)	<0.001	1.38 (1.23, 1.54)	<0.001	1.19 (1.07, 1.32)	0.0013
INR group						
<1.2	1 (ref)		1(ref)		1(ref)	
≥ 0.2	2.07 (1.63, 2.64)	<0.001	2.03 (1.59, 2.60)	<0.001	1.34 (1.01, 1.78)	0.0400

Crude model was adjusted for none. Model I was adjusted for age, gender, and race. Model II was adjusted for age, gender, race, type of intensive care unit for the first time, APACHE-IV scores, heart rate, mean arterial pressure, anion gap, blood urea nitrogen, the use of mechanical ventilation and renal replacement therapy, the admission of vasopressors, aspirin, and heparin, and the transfusion of fresh frozen plasma and platelets.
CA, cardiac arrest; OR, odds ratio; INR, international normalized ratio; APACHE-IV, acute physiology and chronic health evaluation IV.

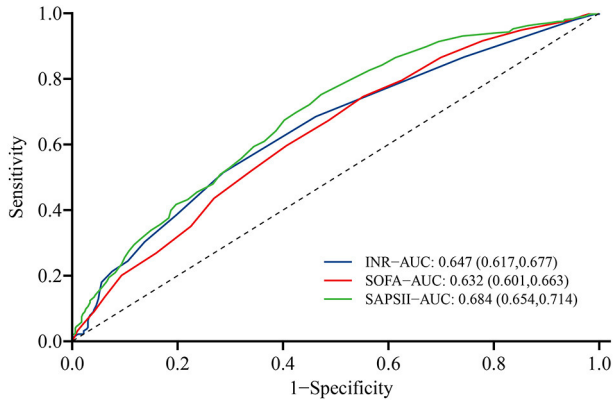

FIGURE 5
Receiver operating characteristic curve of INR (blue), SOFA score (green), and SAPSII score (red) for predicting 1-year all-cause mortality of post-CA patients. CA, cardiac arrest; SOFA, the sequential organ failure assessment; SAPSII, the simplified acute physiology score II.

By contrast, INR is a routine indicator used in most critically ill patients. INR is characterized by being easy and quick to obtain and may have great clinical practicality. We must also note that the discrimination for 1-year all-cause mortality with INR, SOFA and SAPSII scores was not so satisfactory, with the relatively low area under the curve of ROC (0.632–0.684). This is consistent with the previous study. Choi et al. (36) showed that the area under the curve for SOFA and SAPSII scores to predict 30-day mortality of post-CA patients were 0.641 (0.564–0.712) and 0.686 (0.612–0.755), respectively. Besides, for predicting the 1-year all-cause mortality, INR presented the higher specificity, but SOFA and SAPSII scores tended to be higher sensitivity. This showed that in clinical practice, SOFA and SAPSII scores can identify more high-risk patients from critically ill patients, while the application of INR will help reduce the possibility that some low-risk patients may be misjudged as high-risk. And the combination of INR and SOFA or SAPSII score may well be an option to be considered.

The present study had also some limitations. First, this research was a retrospective cohort study, so selection bias was inevitable, and it was difficult to ensure that all variables were evenly distributed across groups. Although multiple regression analysis, PSM, and IPTW were conducted to adjust the confounder and thus improve the reliability of our findings, a prospective cohort study was meaningful to perform for evaluating the relationship between INR and the prognosis of post-CA patients. Second, the relevant data of this study were extracted from a public database, and some recording errors were possible. Third, the research subjects we included were patients admitted to the ICU in the BIDMC from 2008 to 2019. With such a great time span, the diagnosis and treatment may be updated in this period, which may affect the prognosis. Last, the underlying mechanism between elevated INR and increased mortality in post-CA patients remains unclear, and further research is necessary.

5. Conclusions

High levels of INR were closely associated with the poor short- and long-term prognosis in post-CA patients, including 30-day, 90-day, 1-year, and in-hospital all-cause mortalities. INR is expected to be a simple and effective prognostic evaluation indicator.

Data availability statement

Publicly available datasets were analyzed in this study. The data can be extracted from MIMIC-IV database (https://physionet.org/content/mimiciv/2.0/) after passing on the required courses and obtaining the authorization.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LZ and QC conceived and designed the study. YT extracted and analyzed the clinical data. JS drafted the manuscript and assisted in the statistical analysis. ZY, BL, and BP participated in the implementation of statistical methods and put forward constructive suggestions. JM, XZ, and YF reviewed the study and participated in the interpretation of the results. All authors approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1112623/full#supplementary-material

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Prediction of in-hospital death following acute type A aortic dissection

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Background: Our goal was to create a prediction model for in-hospital death in Chinese patients with acute type A aortic dissection (ATAAD).

Methods: A retrospective derivation cohort was made up of 340 patients with ATAAD from Tianjin, and the retrospective validation cohort was made up of 153 patients with ATAAD from Nanjing. For variable selection, we used least absolute shrinkage and selection operator analysis, and for risk scoring, we used logistic regression coefficients. We categorized the patients into low-, middle-, and high-risk groups and looked into the correlation with in-hospital fatalities. We established a risk classifier based on independent baseline data using a multivariable logistic model. The prediction performance was determined based on the receiver operating characteristic curve (ROC). Individualized clinical decision-making was conducted by weighing the net benefit in each patient by decision curve analysis (DCA).

Results: We created a risk prediction model using risk scores weighted by five preoperatively chosen variables [AUC: 0.7039 (95% CI, 0.643–0.765)]: serum creatinine (Scr), D-dimer, white blood cell (WBC) count, coronary heart disease (CHD), and blood urea nitrogen (BUN). Following that, we categorized the cohort's patients as low-, intermediate-, and high-risk groups. The intermediate- and high-risk groups significantly increased hospital death rates compared to the low-risk group [adjusted OR: 3.973 (95% CI, 1.496–10.552), $P < 0.01$; 8.280 (95% CI, 3.054–22.448), $P < 0.01$, respectively). The risk score classifier exhibited better prediction ability than the triple-risk categories classifier [AUC: 0.7039 (95% CI, 0.6425–0.7652) vs. 0.6605 (95% CI, 0.6013–0.7197); $P = 0.0022$]. The DCA showed relatively good performance for the model in terms of clinical application if the threshold probability in the clinical decision was more than 10%.

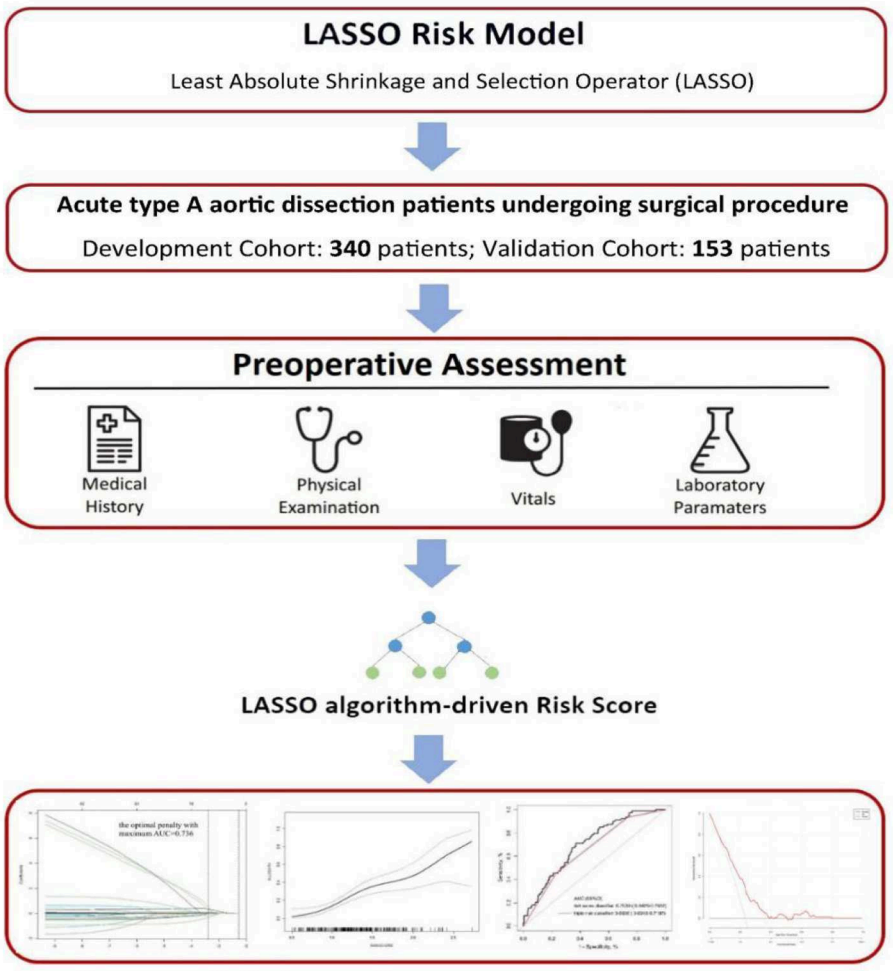
Conclusion: A risk classifier is an effective strategy for predicting in-hospital death in patients with ATAAD, but it might be affected by the small number of participants.

KEYWORDS

in-hospital death, risk prediction, acute type A aortic dissection, prediction model, biomarker

Introduction

Acute type A aortic dissection (ATAAD) is a cardiovascular emergency that poses a serious risk to life and has a greater rate of short-term morbidity and mortality (1). According to estimates, there is a 1%−2% probability of death every hour, and non-operative therapy caused mortality in ∼60% of patients (2, 3). The rate of mortality for patients with ATAAD continued to be as high as 22% according to the latest research



GRAPHICAL ABSTRACT

from the International Registry of Acute Aortic Dissection, which comprised 4,428 individuals from 1995 to 2013 (4).

Acute type A aortic dissection is frequently managed by medical therapy and immediate surgery during the acute stage. The current standard of care for patients with ATAAD is still surgical repair, which has been found to be the most effective therapy, with a mortality rate of 27% compared to 56% for those managed medically in-hospital (5). Despite improvements in perioperative care and surgical procedures, mortality rates remain high (4, 6). Therefore, it is crucial to identify patients with high-risk ATAAD (7).

Although the fact that numerous models have been established to foresee morbidity or mortality in heart surgery (8, 9), there is no golden standard for the prognosis of ATAAD, and there are no predictive models that only use preoperative factors to predict in-hospital death risk after the surgical management of ATAAD.

In order to promote clinical assessment for patient treatments and enhance risk/benefit-based strategic decisions, we conducted a study using preoperative features with the purpose of developing a risk classifier that anticipates in-hospital death in Chinese patients with ATTAD.

Methods

Study design and participants

From 1 January 2016 to 31 December 2021, a single-center, retrospective cohort research was set up. The derivation cohort consisted of 340 consecutive patients with ATAAD who underwent surgery at the Tianjin Chest Hospital (Tianjin, China). To externally validate this model, we used a separate data set of 153 patients with ATAAD (validation cohort) from the First Hospital of Nanjing Medical University (Nanjing, China) between 1 January 2004 and 31 July 2018. The Ethics Committee of the Tianjin Chest Hospital authorized the study with regulatory and ethical

Abbreviations: ATAAD, Acute type A aortic dissection; WBC, white blood cell count; NEUT, neutrophil granulocyte count; LYM, lymphocyte count; MONO, monocyte count; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; BNP, n-terminal pro-brain natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, hypersensitive C-reactive protein; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease; MVA time, mechanical ventilation assistance time.

permission (2023LW-001). It was also approved by the Ethics Committee of the First Hospital of Nanjing Medical University. Due to the retrospective nature, informed written consent was waived. These individuals were not included if they had a history of trauma, pregnancy, iatrogenic aortic dissection, Marfan syndrome, infections, tumors, or other conditions involving the immune and circulatory systems.

Candidate predictors

Medical records were used to collect valid information for almost every patient, and under the constraints of available data, all eligible predictors were chosen based on thorough literature studies and clinical findings. Age at operation, weight, sex, and height constituted the continuous and classified baseline data. The clinical profiles included a history of smoking, drinking, hypertension, diabetes, stroke, chronic obstructive pulmonary disease, and coronary heart disease. White blood cell count, neutrophil granulocyte count, monocyte count, lymphocyte count, hemoglobin, platelet count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte to lymphocyte ratio, n-terminal pro-brain natriuretic peptide, albumin, alanine aminotransferase, aspartate aminotransferase, fibrinogen, hypersensitive c-reactive protein, D-dimer, serum creatinine, estimated glomerular filtration rate, and blood urea nitrogen were all included in the preoperative testing profiles. Intraoperative variables included death, mechanical ventilation assistance time, hospital days, and intensive care unit stay time. Table 1 provides a list of these specific and thorough definitions.

Study outcome

In-hospital death served as the major clinical endpoint. Mechanical ventilation assistance time, hospital days, and ICU stay time are the secondary outcomes.

Statistical analysis

Variables in the derivation and validation cohorts were checked for missing values ahead of data analysis. The percentage of missing data among the predictors ranged from 0 to 31.7%. Using the mice package for R, which embeds predictive mean matching with the cases (k) = 5 default, we imputed incomplete information by multiple imputations using chained equations to include these data throughout the analyses.

The model was carried out in accordance with the recommendations of Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) (10). We added a collection of preset prediction factors for preoperative variables made up of clinical characteristics and data from preoperative testing (Table 1). To choose the most helpful prediction factors from those candidates in the cohorts, we then used the least absolute shrinkage and selection operator (LASSO) analysis in a penalized logistic regression model (R package glmnet) (11). LASSO applies a penalty to variables, ultimately only selecting

TABLE 1 Candidate predictors of 340 patients with ATAAD in the derivation cohort.

Candidate predictors	Survival ($N = 261$)	Death ($N = 79$)	*P*-value
Height (cm)	171.10 ± 7.80	169.73 ± 8.74	0.185
Age (year)	53.11 ± 11.65	54.03 ± 12.78	0.549
Weight (kg)	79.33 ± 16.44	81.03 ± 18.56	0.436
Male, *n* (%)	193 (73.95%)	57 (72.15%)	0.189
WBC, 10^9/L	11.20 ± 3.7	13.42 ± 3.67	<0.001
NEUT, 10^9/L	9.53 ± 3.77	11.66 ± 3.99	<0.001
LYM, 10^9/L	1.04 ± 0.56	1.03 ± 0.61	0.867
MONO, 10^{12}/L	0.57 ± 0.28	0.63 ± 0.24	0.135
HGB, g/L	131.72 ± 22.24	133.53 ± 17.46	0.506
PLT, 10^9/L	181.89 ± 66.98	177.89 ± 50.64	0.624
PLR	215.93 ± 114.11	227.61 ± 161.86	0.473
NLR	12.39 ± 8.28	15.21 ± 11.18	0.016
LMR	2.19 ± 1.50	1.78 ± 0.94	0.023
BNP, pg/ml	116.40 (41.32–422.70)	154.40 (61.71–472.9)	0.351
ALB, g/L	40.00 (37.30–43.00)	39.80 (37.73–41.95)	0.587
ALT, U/L	18.60 (12.20–28.80)	21.20 (14.60–34.70)	0.036
AST, U/L	20.10 (15.40–28.80)	21.90 (16.10–48.75)	0.062
FIB, mg/dl	2.67 (2.19–3.35)	2.43 (1.79–3.16)	0.280
D-Dimer, mg/L	9.28 (2.99–20.00)	14.18 (3.61–20.00)	0.117
CRP, mg/L	7.47 (2.41–23.23)	7.19 (2.97–18.30)	0.393
Scr, mmol/L	94.89 ± 42.77	114.68 ± 71.81	0.003
eGFR, ml/min	95.70 ± 34.29	90.29 ± 48.64	0.27
BUN, mg/dL	6.57 ± 2.42	7.73 ± 4.01	0.002
Drinking, *n* (%)	108 (41.38%)	27 (34.18%)	0.252
Smoking, *n* (%)	136 (52.11%)	44 (55.70%)	0.576
Hypertension, *n* (%)	184 (70.50%)	61 (77.22%)	0.244
Diabetes, *n* (%)	15 (5.75%)	2 (2.53%)	0.251
Stroke, *n* (%)	22 (8.43%)	6 (7.59%)	0.813
COPD, *n* (%)	3 (1.15%)	0 (0.00%)	0.338
CHD, *n* (%)	20 (7.66%)	13 (16.46%)	0.021
Arrhythmia, *n* (%)	9 (3.45%)	2 (2.53%)	0.687
MVA times (hour)	52.00 (17.00–119.00)	85.00 (27.50–239.01)	<0.001
Hospital day (day)	15.00 (11.00–20.00)	11.00 (3.00–16.00)	<0.001
ICU stay time (day)	7.00 (4.00–11.00)	7.00 (3.00–14.50)	0.169

WBC, white blood cell count; NEUT, neutrophil granulocyte count; LYM, lymphocyte count; MONO, monocyte count; HGB, hemoglobin; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; BNP, n-terminal pro-brain natriuretic peptide; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB, fibrinogen; CRP, hypersensitive C-reactive protein; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; CHD, coronary heart disease; MVA time, mechanical ventilation assistance time.

ones that contribute to the out-of-sample performance by utilizing cross-validation. This results in excellent predictive performance in datasets with potential multi-collinearity from many predictor variables and does not rely on *P*-values. Using the product of the expression levels for the variables chosen by the LASSO analysis and the corresponding regression coefficients weighted by logistic regression analysis in the cohort, we established the prediction scoring model by allocating each patient a risk score for postoperative in-hospital death. Afterward, using generalized additive models, we fitted the correlation between the risk score and in-hospital death. Then, we fitted the relationship between the risk score and in-hospital death using generalized additive models and found the optimal cut-off point using EmpowerStats software (X&Y Solutions). The thresholds for the scores that were output from the predictive model that was used to classify patients into different risk categories were defined as the scores with the highest log-likelihood value in a regression model. We divided patients into low-, middle-, and high-risk categories based on the inflection of the risk score curve with in-hospital death. Multiple comparisons of in-hospital death rates against a control group (low-risk category) were conducted using Dunnett's method. In addition, we compared our new model with the prior published nomogram for acute thoracic dissection, and we found that this risk model is significantly superior to Yang's nomogram (12).

In total, 153 patients with ATAAD from the First Hospital of Nanjing Medical University were used as an independent external data set to evaluate the external validity of model performance. We examined the discrimination ability [area under receiver operating characteristic curve (AUC)] and clinical application ability (decision curves), which assess the net benefit of nomogram-assisted decisions. Using logistic regression for baseline data, we subsequently evaluated the relationship between risk classifications and in-hospital death.

For continuous variables, data are displayed as frequencies (percentages) for categorical variables and medians [interquartile ranges (IQRs)]. The χ^2 test or Fisher exact test for categorical variables and the Student *t*-test or the Mann–Whitney U-test for continuous variables analyzed group differences. A two-sided *P*-value of 0.05 was regarded as statistically significant. We conducted the statistical analysis using Stata v14 (StataCorp) and R software (v3.2.0; R Foundation for Statistical Computing).

Results

The derivation cohort comprised 340 patients with ATAAD who had undergone surgical treatment, with a mean age of 53.32 years. Of these patients, 90 were women, constituting 26.47% of the total (Table 1). The validation cohort consisted of 153 patients, with a mean age of 54.67 years and including 39 (46.2%) women (Table 2). The occurrence of in-hospital death was 23.24% (79/340) in the derivation cohort and 15.69% (24/153) in the validation cohort. Baseline clinical characteristics in the cohort are listed in Table 1. In the death group, mechanical ventilation assistance time was much longer than the survival group [median: 85.00 (IQR: 27.50–239.01) vs. 52 (IQR: 17.00–119.00], $P < 0.001$). The hospital day for the death group seemed to be shorter compared to that of the survival group [median: 11.00 (IQR: 3.00–16.00) vs. 15 (IQR: 11.00–20.00), $P < 0.001$]. We later discovered a hybrid panel using the LASSO analysis that included five factors with the optimal k penalty that were related to in-hospital death in the cohort (AUC = 0.736; Table 1, Figure 1). The expression levels of these five factors were weighted by their regression coefficients, and a risk score was calculated for each patient using this procedure:

TABLE 2 Patient characteristics and outcomes in derivation and validation cohorts.

	Derivation cohort ($N = 340$)	Validation cohort ($N = 153$)
In-hospital death	79 (23.24%)	24 (15.69%)
Height (cm)	170.79 ± 8.03	169.42 ± 8.42
Age (year)	53.32 ± 11.91	54.67 ± 12.54
Weight (kg)	79.72 ± 16.94	72.15 ± 12.74
Male, *n* (%)	250 (73.53%)	114 ± 74.51%
WBC, 10^9/L	11.72 ± 3.86	11.15 ± 4.88
NEUT, 10^9/L	10.02 ± 3.92	9.12 ± 4.78
LYM, 10^9/L	1.04 ± 0.57	1.26 ± 0.76
MONO, 10^{12}/L	0.59 ± 0.27	0.72 ± 0.39
HGB, g/L	132.14 ± 21.21	134.29 ± 17.99
PLT, 10^9/L	180.96 ± 63.51	180.16 ± 64.07
PLR	218.64 ± 126.64	178.72 ± 99.12
NLR	13.05 ± 9.10	10.08 ± 8.02
LMR	2.10 ± 1.40	2.17 ± 1.60
BNP, pg/ml	131.40 (51.39–467.55)	486.40 (307.50–927.20)
Albumin, g/L	41.17 ± 24.83	40.13 ± 22.75
ALT, U/L	19.05 (12.60–30.83)	33.66 ± 25.58
AST, U/L	20.40 (15.57–31.45)	49.48 ± 116.12
FIB, mg/dl	2.58 (2.10–3.30)	2.77 ± 1.58
D-Dimer, mg/L	11.37 (3.10–20.00)	6.43 ± 10.88
CRP, mg/L	7.42 (2.51–23.20)	32.84 ± 28.52
Scr, mmol/L	99.49 ± 51.57	92.79 ± 114.34
eGFR, ml/min	94.44 ± 38.10	86.61 ± 35.86
BUN, mg/dL	6.84 ± 2.90	7.30 ± 5.50
Drinking, *n* (%)	135 (39.71%)	59 (38.56%)
Smoking, *n* (%)	180 (52.94%)	55 (35.95%)
Hypertension, *n* (%)	245 (72.06%)	101 (66.01%)
Diabetes, *n* (%)	17 (5.00%)	2 (1.31%)
Stroke, *n* (%)	28 (8.24%)	13 (8.50%)
COPD, *n* (%)	3 (0.88%)	4 (2.61%)
CHD, *n* (%)	33 (9.71%)	15 (9.80%)
Arrhythmia, *n* (%)	11 (3.24%)	1 (0.65%)
MVA times (hour)	57.00 (19.00–133.50)	35.00 (21.00–86.00)
Hospital day (day)	14.00 (10.00–20.00)	21.00 (17.00–29.00)
ICU stay time (day)	7.00 (4.00–12.00)	7.00 (4.00–11.00)

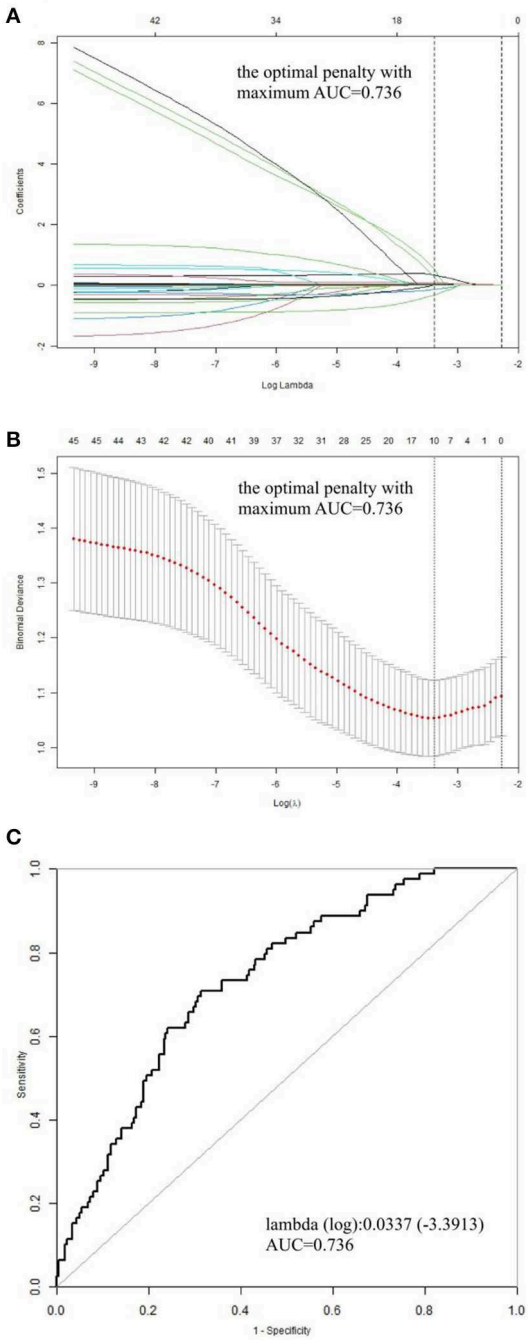


FIGURE 1
Profile charts for the LASSO model. **(A)** The factors and their regression coefficients were chosen for the model based on the optimal k for the LASSO model, and the coefficient profile graphs demonstrate how the size of the preoperative variables' coefficients keeps shrinking with the growing quantity of the k penalty. **(B)** Plotting penalties for the LASSO model. The standard error is displayed as colored error bars. **(C)** The ideal κ penalty for the LASSO model has an AUC maximum of 0.736. AUC, area under the receiver operating characteristic curve; LASSO, least absolute shrinkage and selection operator.

Risk score = 0.00067*Scr + 0.01437*D-Dimer + 0.07890*WBC+ 0.31527*CHD + 0.02788*BUN. Their predictive importance is shown in Supplementary Figure 1 (Scr: serum creatinine; WBC: white blood cell count; CHD: coronary heart disease; BUN: blood urea nitrogen).

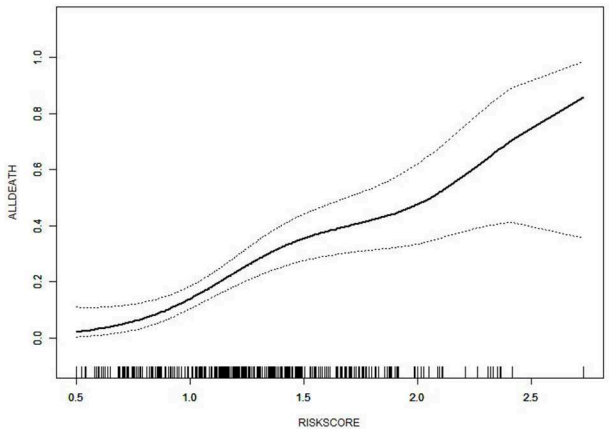


FIGURE 2
Relationship between risk score and in-hospital death.

The in-hospital risk of death was identified as having an increased risk score. Compared to those who survived, patients who died in the hospital had a substantially higher risk score [median: 1.533 (IQR: 1.238–1.742) vs. 1.237 (IQR: 0.977–1.483), $P < 0.001$; Figure 2]. For the likelihood of hospitalized death in the cohort, patients were divided into three risk categories: low risk (1 or fewer points), intermediate risk (between 1 and 1.5 points), and high risk (1.5 points or more). With reference to the low-risk group with 74 (21.8%) patients, the intermediate group with 170 (50.0%) patients and the high-risk group with 96 (28.2%) patients posed a substantially greater risk of postoperative in-hospital death in the cohort [adjusted OR: 3.973 (95% CI, 1.496–10.552), $P = 0.00564$; 8.280 (95% CI, 3.054–22.448), $P = 0.00003$, respectively]. We performed a comparison of the diagnostic value of the continuous and categorical risk scores. According to the AUC comparison, the risk score classifier exhibited better prediction ability than the triple-risk categories classifier [AUC: 0.7039 (95% CI, 0.6425–0.7652) vs. 0.6605 (95% CI, 0.6013–0.7197); $P = 0.0022$] for predicting in-hospital death. For the risk score classifier, the specificity and sensitivity were 0.6322 and 0.7089, and for the triple-risk categories classifier, the specificity and sensitivity were 0.7701 and 0.4557, respectively (Figure 3A). In order to test the risk score classifier's performance, the discrimination was a little lower in the external validation cohort [AUC: 0.6501 (95% CI, 0.5283–0.7719)], and the specificity and sensitivity were 0.7874 and 0.4348 (Figure 3B).

The decision curves for in-hospital death probability in the derivation cohort and validation cohort (Figures 4A, B) showed relatively good performance for the model in terms of clinical application. If the threshold probability in the clinical decision was more than 10%, then the use of the risk score classifier to detect in-hospital death showed a greater advantage than assuming that all patients would develop in-hospital death or that no patients would develop in-hospital death.

Consequently, to predict in-hospital death in patients with ATAAD, the risk score classifier was chosen as the major tool instead of the triple-risk categories classifier.

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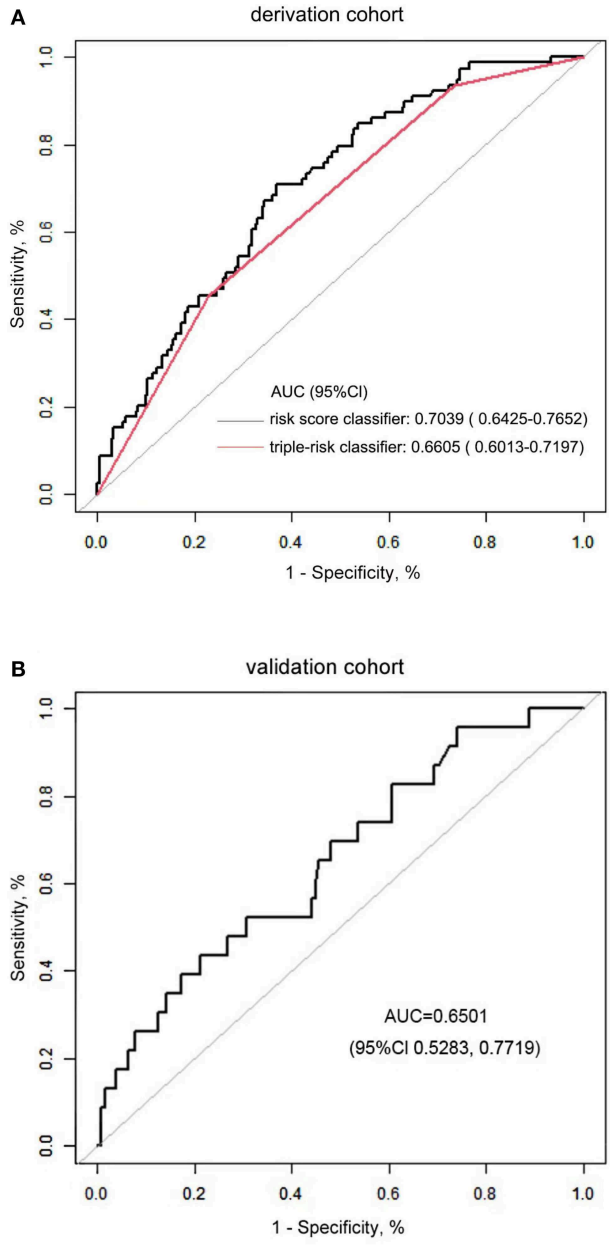

FIGURE 3
(A) Comparison of the risk score classifier and the triple-risk (i.e., low, intermediate, high) classifier. AUC indicates the area under the receiver operating characteristic curve. **(B)** The performance of the risk score classifier in the validation cohort.

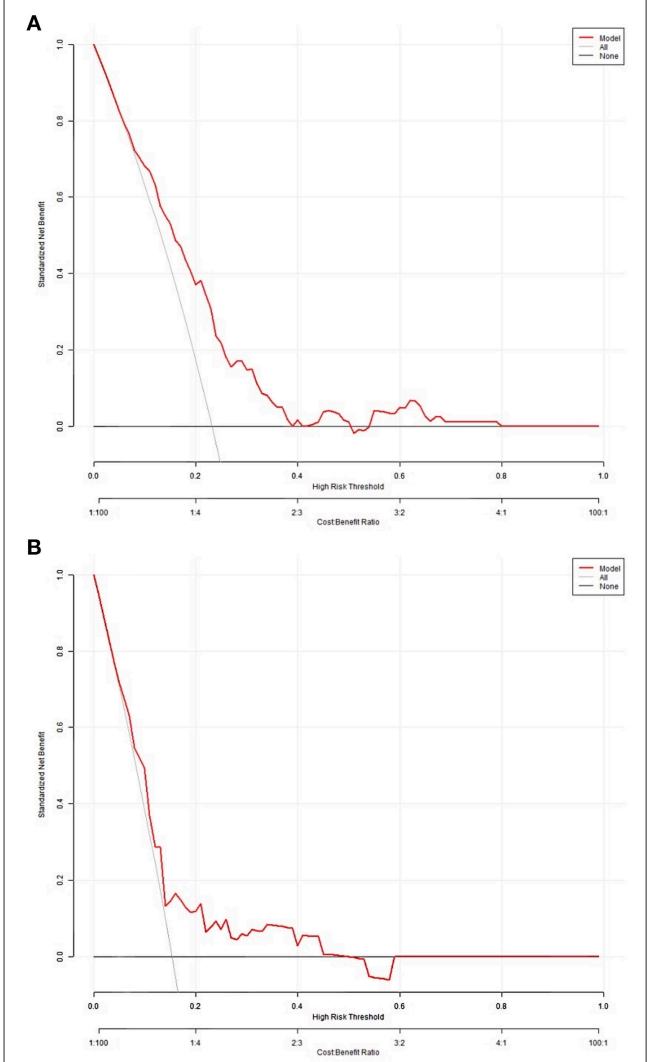

FIGURE 4
Decision curves for in-hospital death probability in the derivation **(A)** and validation cohorts **(B)**.

In addition, we compared our new model with the prior published nomogram for patients with ATAAT, and we found that this risk model is significantly superior to Yang's nomogram (Supplementary Table 1).

Discussion

In this single-center retrospective cohort study, we created a novel predictive algorithm based on five preoperative characteristics chosen to greatly enhance the ability to forecast in-hospital death in Chinese patients with ATAAD. Patients with high-risk ATAAD who underwent surgery may be identified by clinicians using this prediction model. The straightforward application of these fewer variables for early risk-stratification in patients with ATAAD presenting to the emergency department seems to render them appealing, quick, and easy triage tools, especially if their application would result in a quantitatively lower death possibility and better prognoses for patients. The optimized tool showed good discrimination. Our findings demonstrated that patients in the intermediate and high-risk groups exhibited a significantly higher probability of dying in the hospital than those in the low-risk group.

Given that ATAAD is a high-risk disease, progresses rapidly, and has a high mortality rate, it may be possible to develop better predictive and therapeutic methods by investigating the key factors that contribute to and initiate postoperative hospital death. According to the findings of our research, there is a set of five

preoperative factors which could accurately forecast in-hospital death in patients with ATAAD. Patients with higher preoperative levels of Scr, BUN, WBC, and D-dimer and a history of CHD had a higher risk of in-hospital death.

D-dimer is a protein fragment produced by crosslinked fibrin which is detectable in plasma after thrombus fibrinolysis and serves as a biomarker for the synthesis of the coagulation-fibrinolysis balance (13). Aortic dissection and subsequent aortic rupture are brought on by thrombosis and inflammation, and D-dimer is a key factor in thrombosis (14, 15). D-dimer levels below a previously defined cut-off reflect a negligible or non-existent thrombus formation, conversely, the appearance of D-dimer in circulating plasma beyond that of a specified level can, indeed, indicate the likelihood of an unnoticed thrombosis, with values typically assumed to be related to clot burden (15, 16). D-dimer has been demonstrated in recent years to be significant for prognostication in a variety of cardiovascular illnesses (17, 18). D-dimer testing has already been advised for the rule-out of ATAAD since earlier research has demonstrated a strong link between increased D-dimer levels and in-hospital death (19–22). As said by Feng et al., increased D-dimer levels were found to be independently related to in-hospital major adverse events and can, therefore, be employed as a helpful predictive biomarker prior to operation with ATAAD (21). In addition, Tang et al. also discovered that elevated D-dimer is an independent predictor of unfavorable in-hospital outcomes in patients with ATAAD (22). According to the findings of this research, patients with ATAAD may have higher D-dimer levels, which is in line with earlier studies and might be a predictive sign of poor results (20–22), despite the fact that the disparity was not statistically significant, perhaps a larger sample size will be required to test it again.

The inflammatory reaction is a significant contributing factor to the progression of aortic dissection. The inflammatory response could be brought on by the aortic tissue injury and thrombus in the fake lumen generated by the dissection. The tissues of the torn aorta have been found to have WBC, including neutrophils and macrophages (23, 24). The perioperative elevated WBC count (a generator of inflammation) was linked to an increased rate of in-hospital death and was served as a kind of risk variable for a composite adverse event involving heart, lung, brain, and systemic condition. However, The special impact of the WBC on the surgical outcome of TAAAD remained unelucidated. It was said that patients with high preoperative WBC had a poor prognosis and responded worse than those with normal WBC (25, 26). The post-discharge mortality in individuals with ATAAD is independently predicted by relatively high WBC on admission, according to Zhang et al. (27). Ke et al. also said that increased WBC can be employed as supplementary markers for postoperative in-hospital death with ATAAD (28). Elevated preoperative WBC was associated with a higher risk of death following an ATAAD procedure in this research, and this could be caused by inflammation from a vascular intima rupture, just as the difference in WBC between the two groups was statistically significant, which is in line with the findings of the outcomes of past experiments (29).

In recent years, it has been demonstrated that preoperative organ malperfusion influences the prognosis for patients with ATAAD (30), and early renal dysfunction before surgery was common in patients with ATAAD (31). The relationship between the prognostic value of preoperative renal dysfunction and postoperative hospital death in patients with ATAAD has not been explored in the literature. Imasaka discovered that there is no clear link between the preoperative estimated glomerular filtration rate and in-hospital mortality in patients with ATAAD (32). However, concerning in-hospital death among patients with ATAAD, Zhou et al. discovered that moderate and severe renal dysfunction were risk factors (33). Fan et al. discovered that preoperatively elevated SCr is associated with death in patients with ATAAD following surgical treatment (34). In patients with type A aortic dissection, Li et al. revealed that increased blood urea nitrogen levels might be a death risk factor (35). Our study enhanced the impact of preoperative renal impairment on postoperative hospital death among patients with ATAAD using the two variables, SCr and BUN, as the conventional reference index for evaluating renal function. The statistical probability of postoperative in-hospital death increases with considerably greater preoperative levels of Scr and BUN, and this difference is statistically significant, this is consistent with earlier research (36).

When treating ATAAD, it is important to take into account the prevalence of coronary artery disease caused by both the included dissection and atherosclerotic stenosis. Nevertheless, it is still unclear what the connection is between ATAAD and coronary artery diseases. Du et al. found that a history of coronary heart disease had a close relationship with AAD and was an independent risk factor for AAD (37). In our study, the history of CHD is associated with postoperative hospital death, and the difference is statistically significant, which is consistent with the results of previous literature (28, 38). However, patients with a history of CHD appeared to be more prevalent in the survival ATAAD group, and we think this may be due to the small sample size.

The limitations of this research should be taken into consideration when evaluating our final results. First, this research is a retrospective single-centered study, which could lead to selection bias. Second, the model does not incorporate enough risk factors. Therefore, more risk factors should be included in the following validation studies to further improve the predictive ability of the model. Third, while the study's operational approach was chosen by weighing up the hazards and advantages of every operation against the available baseline parameters and the inclinations of the cardiologists participating, their specialist skills may not have been the same as those of other practitioners, which could limit the generalizability of these findings in relation to other hospitals. Consequently, in the future, a prospective multicenter large-scale study will always be required to assess the effectiveness of the present findings ahead of their being implemented in the clinical setting.

Conclusion

In this study, we effectively created a prediction model for in-hospital death in Chinese patients with ATAAD using preoperative indicators. Our results indicate that the risk classifier can also successfully divide patients into various risk categories

for in-hospital death, greatly enhancing predictive ability for the evaluation of clinical outcomes. In addition, we successfully demonstrated that the overall risk score classifier that might have been optimized could have significantly improved predictive accuracy for identifying patients who might suffer in-hospital death with ATAAD. The classifier would then assist clinicians in choosing a highly customized treatment strategy for patients with ATAAD. Nevertheless, it is extremely important to keep in mind that the individuals who participated in this research were all subjected to a type of operation that is particularly uncommon in a significant portion of the rest of the globe. In order to validate our conclusion, we anticipate enlarging the sample in subsequent research and performing a prospective cohort study.

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 the Ethics Committee of Tianjin Chest 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

ZG contributed to the conception of the study and revise the manuscript. JC and MQ contributed significantly to the collection and assembly of data. JC and YB performed the data analysis and wrote the manuscript. YB helped perform the analysis with the constructive discussion. HL provided the validation cohort data and helped revise the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1143160/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Feature of importance in the derivation cohort.

SUPPLEMENTARY TABLE 1
Compare LASSO risk model with previous nomogram model in derivation cohort.

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C-reactive protein to lymphocyte ratio is a significant predictive factor for poor short-term clinical outcomes of SARS-CoV-2 BA.2.2 patients

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Objective: The aim of the present study is to assess the utility of C-reactive protein to Lymphocyte Ratio (CLR) in predicting short-term clinical outcomes of patients infected by SARS-CoV-2 BA.2.2.

Methods: This retrospective study was performed on 1,219 patients with laboratory-confirmed SARS-CoV-2 BA.2.2 to determine the association of CLR with short-term clinical outcomes. Independent Chi square test, Rank sum test, and binary logistic regression analysis were performed to calculate mean differences and adjusted odds ratios (aORs) with their 95% CI, respectively.

Results: Over 8% of patients admitted due to SARS-CoV-2 BA.2.2. were critically ill. The best cut-off value of CLR was 21.25 in the ROC with a sensitivity of 72.3% and a specificity of 86%. After adjusting age, gender, and comorbidities, binary logistic regression analysis showed that elevated CLR was an independent risk factor for poor short-term clinical outcomes of COVID-19 patients.

Conclusion: C-reactive protein to Lymphocyte Ratio is a significant predictive factor for poor short-term clinical outcomes of SARS-CoV-2 BA.2.2 inflicted patients.

KEYWORDS

SARS-CoV-2 BA.2.2, C-reactive protein to lymphocyte ratio, cut-off value, clinical outcomes, multivariate logistic regression

1. Introduction

The 2019 corona virus disease (COVID-19) has elicited global chaos, whereas a novel Omicron variant has challenged the healthcare system (1). This variant has been referred to as a variant of concern (VOC) by the World Health Organization (WHO), owing to its alarming transmission and infectivity rate (2, 3). Currently, 26 countries are infected by Omicron variants (3). In late February, 2022, a wave of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection rapidly appeared in Shanghai, China. Genomic analysis showed that the

SARS-CoV-2 BA.2.2 sub-lineage was the responsible pathogen (4). Of note, BA.2 is a sub-lineage of the Omicron variant of SARS-CoV-2 (B.1.1.529). Although Omicron BA.2 evolves toward less virulence, a large percentage of patients with severe conditions have been reported in the unvaccinated population, especially in elderlies (5). How to translate the knowledge on COVID-19 into prevention and therapeutic strategies for Omicron variants is a problem we need to face now and in the future. In this retrospective study, we set to explore the potential of early triage using results of routine tests.

It is essential to early assess and classify disease severity in order to improve patients' clinical outcomes. At the same time, classification can also help clinicians find patients who may have aggravated conditions as soon as possible. It is more beneficial to allocate limited medical resources to people who need more active treatments. Therefore, clinicians need more valuable laboratory indicators that can help to assess disease severity at the early stage of infection. One of the characters of COVID-19 is the systemic inflammatory response to the SARS-CoV-2 infection. Nearly all patients admitted to the hospital due to COVID-19 have anomalies in these inflammatory biomarkers (6). Recent studies have demonstrated an association between elevated levels of CRP and the severity of COVID-19 (7–11). Some studies even showed that the level of CRP was correlated with poor clinical outcomes among COVID-19 patients (6, 8, 12). Interestingly, some patients, particularly severe COVID-19 patients, showed a low lymphocyte (LYM) count in the full blood count (13–15). Studies have suggested that the degree of lymphocyte count reduction correlates with disease severity in patients with COVID-19 (14, 16, 17). It has been proposed that the ratio of CRP to lymphocytes is the best predictor of survival in patients with malignant tumors based on their inflammatory continuous prognostic score (18–20). A previous study has reported that CRP to Lymphocyte Ratio (CLR) and CRP might be better than LYM alone in assessing patients with severe COVID-19 because CLR is a highly sensitive measure to evaluate the severity of COVID-19 in the early phase (21). However, the sample size of that study was small and the association between CLR and patients' outcomes was not explored. In this retrospective study, it is our aim to evaluate the effectiveness and clinical applicability of CLR in predicting clinical outcomes of SARS-CoV-2 BA.2.2 patients during their admission.

2. Materials and methods

2.1. Study population and design

This study is a single-center, retrospective, observational study on confirmed COVID-19 patients who were admitted to Shanghai Fourth People's Hospital affiliated to Tongji University between 12th April, 2022 and 17th June, 2022. The diagnosis of COVID-19 was confirmed using PCR tests. Patients with positive SARS-CoV-2 BA.2.2 PCR tests were included in the present study. Patients were excluded if they met any of the following criteria: (1) < 18, or > 80 years; (2) missing blood cell counts or C-reactive protein results; (3) COVID-19 genotyping was impossible because of hospital stay less than 24 h or absence of CT to scan the lungs (Figure 1). The present study was approved by the human ethics committee of Shanghai Fourth People's Hospital and written informed consent was waived due to the nature of being a retrospective study.

2.2. Data collection

Data were collected from electronic medical records of hospitalized patients, including demographic data, such as age, gender, and concomitant conditions like hypertension, coronary heart disease, atrial fibrillation, diabetes, stroke, dementia, as well as parkinsonism, therapies like oxygen support, antiviral therapy, and use of corticosteroids, laboratory data, such as red blood cell counts, white blood cell counts, neutrophil counts, monocyte counts, lymphocyte counts, platelet counts of the peripheral blood, levels of hemoglobin in the plasma and levels of serum CRP, alanine transaminase, aspartate aminotransferase, creatinine, lactate dehydrogenase, troponin-I, d-dimer, procalcitonin, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR), and CLR, which were obtained within 24 h of admission. All patients were followed up during their admission period and their outcomes, such as death or being discharged were recorded. Some patients were admitted twice during the study period due to the repeated procedures of admission, and the worse outcome was used for final analysis. The primary outcome in this study was severe or critical conditions during admission.

The COVID-19 clinical genotyping criteria complied with those from China's official clinical guidelines. Adults can be diagnosed with severe COVID-19 if they met any of the following criteria: (1) shortness of breath, breathing rate greater than or equal to 30 times/min; (2) oxygen saturation is less than or equal to 93% during air inhalation at rest; (3) the ratio of arterial partial pressure of oxygen (PaO_2) to oxygen concentration (FiO_2) < 300 mmHg; PaO_2/FiO_2 was adjusted using a formula which is for correction at high altitudes (eg above 1,000 m): $PaO_2/FiO_2 \times [760/\text{atmospheric pressure (mmHg)}]$. (4) patients whose conditions progressively deteriorated and lesions on lung imaging significantly expanded by >50% within 24–48 h. Critical COVID-19 can be diagnosed if patients presented with one of the following conditions: (1) respiratory failure and the need for mechanical ventilation; (2) the appearance of shock; and (3) intensive care and treatment initiated due to other complications, such as other organ failure.

2.3. Statistical analysis

Continuous variables were expressed in the form of median and interquartile range (IQR) or mean ± SD, whereas categorical variables were expressed in the form of absolute numbers and frequencies (%). Results were compared between groups using either independent sample *t*-tests, or Mann–Whitney U-tests, or Chi-square or Fischer's exact tests as required. Receiver operating characteristic (ROC) curve was used to assess the severity of COVID-19. Youden index was used to evaluate the authenticity of screening tests. The value corresponding to the maximum Youden index is taken as the cut-off value. Models of multivariate logistic regression were built to calculate the odds ratios (ORs), adjusted ORs, and their corresponding 95% CIs for correlations between CLR and clinical outcomes. Confounding factors for these models were selected based on published literatures and clinical judgment, focusing on variables that might confound the relationship between CLR and clinical outcomes. Models were first adjusted for gender and age (model A), and then adjusted for other confounders, such

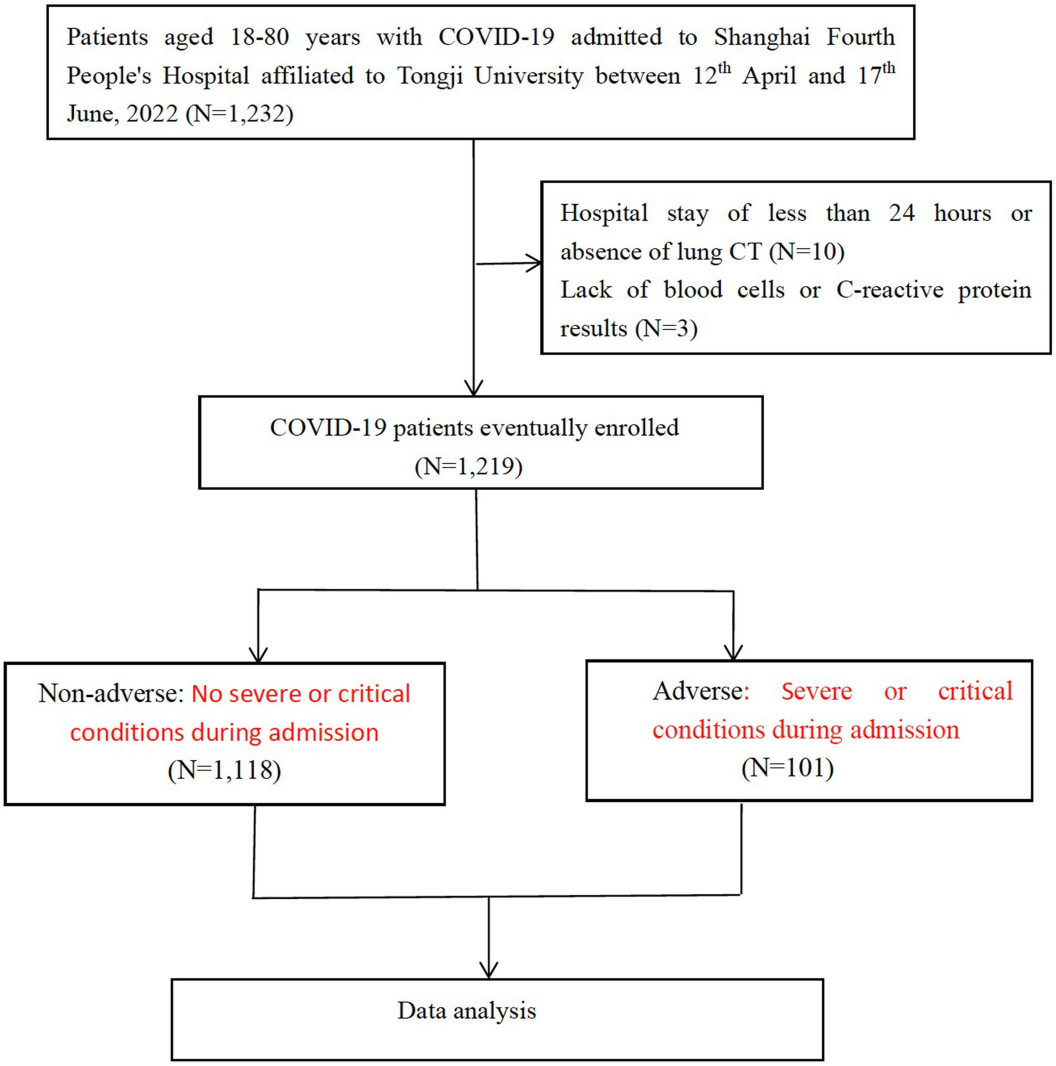

FIGURE 1
Flow chart of patient recruitment, clinical screening, and evaluation.

as hypertension, coronary artery disease, atrial fibrillation, diabetes, stroke, dementia, and parkinsonism (model B). In model C, age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, history of stroke, dementia, parkinsonism, oxygen support, antiviral therapy, and use of corticosteroid were adjusted. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 22). Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Participant characteristics

A total of 1,232 COVID-19 patients met the inclusion criteria and were included in the present study. Three patients who lacked blood cell counts or CRP results, 10 who were unable to complete COVID-19 genotyping due to the length of hospital stay less than 24 h or lack of pulmonary CT examination were excluded. In the end, 1,219 patients were enrolled. The selection process was shown in Figure 1, and baseline characteristics of included patients were shown in Table 1.

In the present study, 101 patients (8.3%) had adverse outcomes. Percentages of male and female patients in the adverse outcome group were comparable to those in the non-adverse outcome group, but there were significantly more males than females in the adverse outcome group, and the average age of patients in the adverse outcome group was larger than that in the non-adverse outcome group. These differences were statistically significant ($p < 0.05$). Regarding concomitant comorbidities, percentages of hypertension, dementia, stroke, and Parkinson's disease in the adverse outcome group were significantly larger than those in the non-adverse outcome group ($p < 0.05$). In terms of treatment, oxygen support and use of corticosteroids showed statistical difference, while antiviral therapy showed no significant difference between adverse and non-adverse outcomes. Levels of CRP, leukocyte counts, neutrophil counts, alanine transaminase, aspartate aminotransferase, lactate dehydrogenase, troponin-I, d-dimer, and procalcitonin were significantly higher in patients with adverse outcomes than those

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TABLE 1 Baseline characteristics of patients with adverse and non-adverse outcomes.

Variables	Total patients	Non-adverse	Adverse	*p* value
Patients, *n* (%)	1,219 (100%)	1,118 (91.7%)	101 (8.3%)	
Sex, *n* (%)				0.011
Female	619 (50.8%)	580 (51.9%)	39 (38.6%)	
Male	600 (49.2%)	538 (48.1%)	62 (61.4%)	
Age, median (IQR), years	68 (60,73)	67 (59,73)	71 (66,76)	<0.001
Comorbidities, *n* (%)				
Hypertension	429 (35.2%)	382 (34.2%)	47 (46.5%)	0.013
Diabetes	228 (18.7%)	203 (18.2%)	25 (24.8%)	0.104
Cardiovascular disease	17 (1.4%)	14 (1.3%)	3 (3%)	0.161
Atrial fibrillation	26 (2.1%)	23 (2.1%)	3 (3%)	0.470
History of stroke	115 (9.4%)	86 (7.7%)	29 (28.7%)	<0.001
Dementia	28 (2.3%)	17 (1.5%)	11 (10.9%)	<0.001
Parkinsonism	16 (1.3%)	12 (1.1%)	4 (4%)	0.037
Laboratory testing				
CRP, mg/L	5.55 (2.06,15.9)	4.85 (1.86,12.86)	49.25 (21.19,162.06)	<0.001
White blood cell count, ×10^9/L	5.27 (4.23,6.78)	5.20 (4.21,6.66)	6.64 (5.01,9.37)	<0.001
Neutrophil count, ×10^9/L	3.18 (2.32, 4.47)	3.08 (2.27,4.30)	4.83 (3.57,7.84)	<0.001
Lymphocyte count, ×10^9/L	1.39 (0.96,1.87)	1.43 (1.01,1.89)	0.82 (0.52,1.40)	<0.001
Monocyte count, ×10^9/L	0.42 (0.32,0.56)	0.42 (0.33,0.56)	0.38 (0.28,0.57)	0.100
Platelet count, ×10^9/L	185 (145, 231)	186.50 (146.75,233)	172 (130, 216.50)	0.023
Red blood cell count, ×10^12/L	4.32 (3.97, 4.70)	4.34 (3.99, 4.70)	4.17 (3.57,4.70)	0.005
Hemoglobin, g/L	129 (119,140)	130 (120,140)	125 (104.50,139)	0.005
Alanine transaminase, U/L	18.85 (13.33,28.54)	18.63 (13.29,27.74)	22.56 (13.80,37.29)	0.035
Aspartate aminotransferase, U/L	23.08 (18.42,30.04)	22.62 (18.22,29.12)	35.30 (23.01,56.25)	<0.001
Creatinine,μmoI/L	56.80 (47.80,69.90)	57.05 (48.20,69.50)	53.90 (41.40,74.30)	0.092
Lactate dehydrogenase, U/L	182.78 (146.25,216.69)	181.04 (145.37,210.76)	228.69 (154.87,296.35)	<0.001
Troponin-I,μg/L	0.01 (0.00,0.02)	0.01 (0.00,0.02)	0.02 (0.01,0.03)	<0.001
D-dimer, mg/L	0.40 (0.26,0.76)	0.37 (0.25,0.63)	1.34 (0.77,2.32)	<0.001
Procalcitonin, μg/L	0.02 (0.02,0.03)	0.02 (0.02,0.02)	0.19 (0.03,0.71)	<0.001
NLR	2.33 (1.46,3.72)	2.20 (1.42,3.46)	5.63 (2.85,12.89)	<0.001
PLR	133.07 (99.15,189.06)	130.12 (97.26,184.49)	194.44 (121.80,314.03)	<0.001
MLR	0.29 (0.21,0.48)	0.28 (0.21,0.46)	0.45 (0.27,0.80)	<0.001
CLR, mg/10^9	4.25 (1.35,13.87)	3.70 (1.22,10.42)	59.60 (15.89,242.74)	<0.001
Therapies				
Oxygen support				<0.001
No oxygen support	850 (69.7%)	835 (74.7%)	15 (14.9%)	
Ordinary oxygen support	319 (26.2%)	278 (24.9%)	41 (40.6%)	
Non-normal oxygen support	50 (4.1%)	5 (0.4%)	45 (44.5%)	
Antiviral therapy	877 (71.9%)	803 (71.8%)	74 (73.3%)	0.757
Use of corticosteroid	63 (5.2%)	24 (2.1%)	39 (38.6%)	$p < 0.01$

NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio; and CLR, C-reactive protein lymphocyte ratio. Ordinary oxygen support: normal nasal tube oxygen; Non-normal oxygen support: high flow oxygen or ventilator-assisted oxygen; Antiviral therapy: the antiviral drug is Paxlovid.

without adverse outcomes. Lymphocyte counts, monocyte counts and platelet count, red blood cell counts, and levels of hemoglobin and creatinine were relatively lower in patients with adverse outcomes than those without adverse outcomes. Apart from the mononuclear cell count and creatinine, other differences were also statistically significant ($p < 0.05$). Furthermore, patients with adverse outcomes had the largest increase in CRP and the most significant decrease in lymphocyte counts.

3.2. Comparison of the area under ROC curve of lymphocyte counts, CRP, and CLR

As shown in Table 2, the effectiveness of CRP, LYM, and CLR in predicting adverse outcomes was compared, and the areas under the receiver operating characteristic curves (ROC) were 0.872, 0.724, and 0.877, respectively. The ROC of CLR was the largest (Figure 2), with a cut-off value of 21.25, a sensitivity of 72.3% and a specificity of 86%.

3.3. Patient characteristics associated with the cut-off value of CLR

In Table 3, included patients were divided into two groups according to the cut-off value of CLR (21.25). There were 229 patients whose ROC was greater than the cut-off value (high group) and 990 smaller than the cut-off value (low group), accounting for 18.8 and 81.2%, respectively. The proportion of male patients in the high group was significantly larger than that in the low group, and similar phenomenon was observed in the average age ($p < 0.05$). Regarding concomitant comorbidities, there were significant differences in diabetes, stroke, and Parkinson's disease ($p < 0.05$). In terms of treatment, oxygen support and use of corticosteroids showed statistical difference, while antiviral therapy showed no significant difference between adverse and non-adverse outcome groups ($p < 0.05$). In laboratory tests, significant differences were observed in CRP, white blood cell counts, lymphocyte counts, monocyte counts, platelet counts, red blood cell counts, and levels of hemoglobin, aspartate aminotransferase, creatinine, lactate dehydrogenase, troponin-I, d-dimer, procalcitonin, NLR, PLR, MLR, and CLR ($p < 0.05$).

3.4. Association of CLR with adverse clinical outcomes

In Table 4, clinical outcomes were compared between the high and the low groups. It was found that the percentages of adverse outcomes were 31.9 and 2.8%, respectively. The proportions of severely and critically ill patients were 27.1 and 2.3%. These differences between the two groups were significant ($p < 0.001$).

3.5. Correlation between CLR and the risk of adverse outcomes

In Table 5, the logistic regression model was used to evaluate the correlation between CLR (below/above CLR cut-off) and the risks of adverse clinical outcomes (severe/critical) in COVID-19 patients. Model A: age, sex-adjusted; Model B: multivariate-adjusted, including age, sex, hypertension, atrial fibrillation, history of stroke, dementia, and Parkinsonism. Model C: Including age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, history of stroke, dementia, parkinsonism, oxygen support, antiviral therapy, and use of corticosteroids. From these four models, it could be seen that CLR with a cut-off value of 21.25 was a potential predictor for adverse outcomes. Regarding adverse outcomes, the unadjusted odds ratio (OR) was 16.08, and the adjusted OR (aOR) after adjusting age and sex (Model A) was 17.09, and the aORs of the multi-factor adjusted models (model B and model C) were 17.04 and 12.29, suggesting that a large CLR was significantly associated with a high risk of poor prognosis.

4. Discussion

2019 corona virus disease has been ongoing for 3 years. Although vaccination among the general population has significantly decreased disease mortality and even the incidence in various regions (22), there are still challenges in confronting the uncertainties introduced by recently identified variants of the COVID-19 virus. It is the experience of multiple clinical centers that the systemic inflammatory panel could reliably predict the exacerbation of this disease 20 days before its occurrence (23, 24). If previously reported approaches can be applied to patients infected by Omicron variants, priorities of receiving specialized treatments can be allocated to those whose conditions are deteriorating. The goal of the present study was to explore the characteristics of Omicron variant inflicted patients and predict their outcomes based on previous knowledge and experience. The baseline data of the present study (Table 1) showed that there were 101 patients (8.3%) with poor prognosis (including severe illness, critical illness) among COVID-19 patients aged between 18 and 80. Although the rate of critical illness was not high in the entire population of COVID-19 patients, it is important to note that patients with adverse outcomes were more likely to be males, older elderlies and those who have multiple comorbidities.

It has been reported that systemic inflammation due to COVID-19 infection leads to immune suppression and apoptosis of lymphocytes (25). This might be the result of direct cytotoxicity of this virus to lymphocytes as this virus was found present in circulating lymphocytes (19, 26). However, the level of CRP has been shown to rise earlier than either lymphopenia or neutrophilia (27). CRP, a super-early reactive protein, is considered to be a hallmark of response to inflammatory cytokines associated with monocyte or macrophage activation, and its expression is increased in inflammatory conditions (21). In certain cases, CRP can activate the complement system, further augmenting the release of inflammatory cytokines, exacerbating tissue damage (28). Therefore, the significantly elevated CRP may reflect the severity of inflammation, whereas lymphopenia is associated with suppressed

TABLE 2 Characteristics of ROC curves in COVID-19 patients.

	ACU (95%CI)	SE	Youden index	Cut-off	Sensitivity	Specificity	*p* value
CRP	0.872 (0.838–0.907)	0.018	0.62	15.75	82.2%	79.8%	<0.001
LYM	0.724 (0.668–0.780)	0.029	0.369	1.065	71.6%	65.3%	<0.001
CLR	0.877 (0.843–0.910)	0.017	0.583	21.25	72.3%	86%	<0.001

SE, standard error; CRP, C-reactive protein; LYM, lymphocyte count; and CLR, the ratio of C-reactive protein to Lymphocyte count.

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TABLE 3 Baseline characteristics of patients stratified by CLR.

Variables	Total patients	CLR<21.25	CLR≥21.25	*p* value
Patients, *n* (%)	1,219	990 (81.2%)	229 (18.8%)	
Sex, *n* (%)				<0.001
Female	619 (50.8%)	558 (56.4%)	61 (26.6%)	
Male	600 (49.2%)	432 (43.6%)	168 (73.4%)	
Age, median (IQR), years	68 (60,73)	67 (59,73)	69 (62,75)	0.002
Comorbidities, *n* (%)				
Hypertension	429 (35.2%)	342 (34.5%)	87 (38%)	0.325
Diabetes	228 (18.7%)	168 (17%)	60 (26.2%)	0.001
Cardiovascular disease	17 (1.4%)	15 (1.5%)	2 (0.9%)	0.754
Atrial fibrillation	26 (2.1%)	20 (2%)	6 (2.6%)	0.61
History of stroke	115 (9.4%)	73 (7.4%)	42 (18.3%)	<0.001
Dementia	28 (2.3%)	20 (2.0%)	8 (3.5%)	0.18
Parkinsonism	16 (1.3%)	9 (0.9%)	7 (3.1%)	0.019
Laboratory testing				
CRP, mg/L	5.55 (2.06,15.9)	4.00 (1.57,8.56)	57.09 (33.91,113.58)	<0.001
White blood cell count, ×10^9/L	5.27 (4.23,6.78)	5.14 (4.19,6.36)	6.61 (4.51,8.99)	<0.001
Neutrophil count, ×10^9/L	3.18 (2.32,4.47)	2.99 (2.18,4.04)	4.88 (3.27,7.36)	<0.001
Lymphocyte count, ×10^9/L	1.39 (0.96,1.87)	1.50 (1.09,1.93)	0.88 (0.61,1.27)	<0.001
Monocyte count, ×10^9/L	0.42 (0.32,0.56)	0.41 (0.32,0.54)	0.47 (0.33,0.64)	0.003
Platelet count, ×10^9/L	185 (145, 231)	187 (148,232.25)	172 (133.5,230.5)	0.04
Red blood cell count, ×10^12/L	4.32 (3.97,4.70)	4.37 (4.04,4.73)	4.15 (3.57,4.62)	<0.001
Hemoglobin, g/L	129 (119,140)	131 (121,140.25)	122 (106,137.50)	<0.001
Alanine transaminase, U/L	18.85 (13.33,28.54)	18.73 (13.36,27.68)	19.46 (12.80,32.05)	0.417
Aspartate aminotransferase, U/L	23.08 (18.42,30.04)	22.50 (18.25,28.89)	26.66 (19.22,43.00)	<0.001
Creatinine,μmoI/L	56.80 (47.80,69.90)	56.35 (47.90,68.08)	60.80 (46.60,78.40)	0.029
Lactate dehydrogenase, U/L	182.78 (146.25,216.69)	179.50 (144.30,206.00)	208.50 (154.70,260.50)	<0.001
Troponin-I,μg/L	0.01 (0.00,0.02)	0.01 (0.00,0.01)	0.01 (0.01,0.02)	<0.001
D-dimer, mg/L	0.40 (0.26,0.76)	0.35 (0.24,0.57)	0.91 (0.47,1.64)	<0.001
Procalcitonin, μg/L	0.02 (0.02,0.03)	0.03 (0.02,2.53)	0.09 (0.02,0.36)	<0.001
NLR	2.33 (1.46,3.72)	2.01 (1.33,3.00)	5.27 (3.29,9.42)	<0.001
PLR	133.07 (99.15,189.06)	124.24 (93.53,172.71)	195.05 (129.27,307,14)	<0.001
MLR	0.29 (0.21,0.48)	0.34 (0.27,1.83)	0.67 (0.51,9.40)	<0.001
CLR, mg/10^9	4.25 (1.35,13.87)	2.79 (1.09,7.13)	59.60 (32.94,126.29)	<0.001
Therapies				
Oxygen support				<0.001
No oxygen support	850 (69.7%)	743 (75.1%)	107 (46.7%)	
Ordinary oxygen support	319 (26.2%)	232 (23.4%)	87 (38.0%)	
Non-normal oxygen support	50 (4.1%)	15 (1.5%)	35 (15.3%)	
Antiviral therapy	877 (71.9%)	721 (72.8%)	156 (68.1%)	0.153
Use of corticosteroid	63 (5.2%)	27 (2.7%)	36 (15.7%)	<0.001

NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio; CLR, C-reactive protein lymphocyte ratio Ordinary oxygen support: Normal nasal tube oxygen, Non-normal oxygen support: High flow oxygen or ventilator-assisted oxygen. Antiviral therapy: the antiviral drug is Paxlovid.

immune function and adverse outcomes of COVID-19 patients, and CLR may be more sensitive in capturing the early part of the inflammatory cascade than other biomarkers as previously reported (19, 21, 26–28). Our study on Omicron BA.2.2 further verified that CLR was more superior (Table 2) to CRP or Lymphocyte counts alone, evidenced by its cutoff value of 21.25 demonstrating a sensitivity of 72.30% and a specificity of 86%. The area under the ROC (AUC) of CLR was 0.877 (95%CI: 0.843–0.910), and it was the largest compared

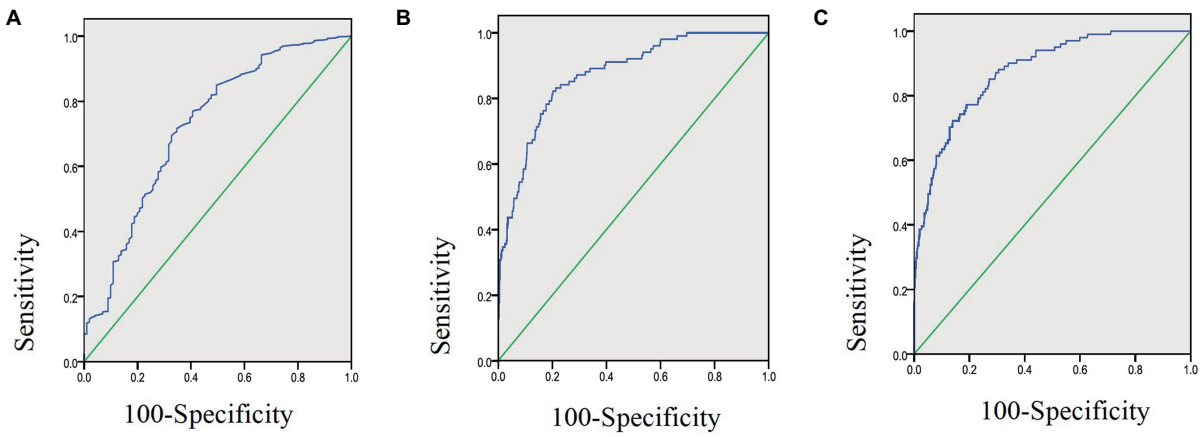

FIGURE 2
Area under ROC curve of lymphocyte count **(A)**, CRP **(B)**, and CLR **(C)** in 1,219 COVID-19 patients aged 18–80years.

TABLE 4 Association between CLR and clinical outcomes.

	CLR<21.25 (*N*=990)	CLR≥21.25 (*N*=229)	*p* value	Chi-square value
Adverse outcomes	28 (2.8%)	73 (31.9%)	$p < 0.001$	206.532
Non-adverse	962 (97.2%)	156 (68.1%)		

CLR: the ratio of C-reactive protein to Lymphocyte count.

TABLE 5 Correlation between CLR and the risks of adverse clinical outcomes.

	Adverse clinical outcomes		
	[a]OR	95%CI	*p* value
Unadjusted	16.08	10.08–25.66	<0.001
Age, sex-adjusted (Model A)	17.09[a]	10.33–28.28	<0.001
Multivariate 1-adjusted (Model B)	17.04[a]	10.07–28.83	<0.001
Multivariate 2-adjusted (Model C)	12.29[a]	6.24–24.20	<0.001

Model A: adjusted for age and gender. Model B: adjusted for multivariable, including age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, history of stroke, dementia, and parkinsonism. Model C: including age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, history of stroke, dementia, parkinsonism, oxygen support, antiviral therapy, and use of corticosteroid. [a]OR represents adjusted OR valule.

with that of CRP or Lymphocyte counts alone (Figure 2). Our results showed that CRP had a predictive sensitivity of 82.2% for adverse prognosis after Omicron infection. Therefore, we suggest that CRP should be used to screen severe COVID-19 patients and CLR should be used to predict the prognosis of patients at the early stage. These two indicators are easy and soon to obtain from every patient, which will facilitate early patient triage and save limited medical resources.

Consistent with what was previously reported in Wuhan, China (21), the present study found significant differences in gender and age between the two groups of patients with the CLR above 21.25 group having significantly more males and older patients than the CLR below 21.25 group. In addition, this is the first report on the association between neurological comorbidities and the prognosis of COVID-19 patients evidenced by the significant difference in stroke and Parkinson's disease between these two groups. Furthermore, the association between CLR and adverse outcomes found in the present study and the regression analysis suggests that CLR is an independent risk factor for poor prognosis of Omicron BA.2.2 patients at the cut-off value of 21.25. Our findings imply that CLR is a more sensitive biomarker than CRP or the lymphocyte count alone in predicting patients' prognosis after COVID-19 infection. This might be applied to other infectious conditions or inflammatory conditions.

4.1. Limitations

A number of limitations were present in our study. First, it is a single center, retrospective study. Therefore, selection bias and other limitations may confine the extrapolation of our conclusion. For example, only some commonly observed confounders were included in the multivariate regression analyses. Second, the present study aimed to focus on findings at admission as predictive markers for adverse outcomes, hence our multivariate regression analyses did not include the type and timing of treatments as variables, which may impact clinical outcomes of COVID-19 patients. In a meta-analysis study, it was found from 44 studies including 20,197 patients that corticosteroids were beneficial for short-term mortality and for mechanical ventilation (29). Third, CLR was only assessed at admission to hospital. The impact of dynamic changes of CRP, lymphocyte counts on clinical outcomes was not evaluated. Additionally, lymphopenia was shown in the full blood test, but which subtypes of lymphocytes were decreased were not known. Further investigations on this may provide deeper insight into disease progression mechanisms and estimation of clinical outcomes of COVID-19 patients. In spite of these limitations, our conclusion was drawn from a relatively large population and the findings were consistent with those of previous studies (21, 26, 27). Furthermore, we have analyzed more clinical and biochemical parameters in our

regression model. There are not many studies on this new strain of Omicron. Therefore, this study has its own innovative characters.

5. Conclusion

The present study found that the overall rate of adverse outcomes (severely or critically ill) after Omicron BA.2.2 infection in adults aged 18–80 years is not high. CRP increased the most and lymphocyte count decreased the most within 24 h after admission. CLR is better than CRP or LYM alone in predicting poor prognosis. The cutoff value of CLR 21.25 is an independent predictor of poor prognosis of Omicron BA.2.2 inflicted patients. Early application of this CLR cut-off value to predict poor prognosis is conducive to patient triage and allocation of medical resources.

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

This study involving human participants were reviewed and approved by the Human Ethics Committee of Shanghai Fourth People's Hospital.

Author contributions

YB and YW conceived this study. BX and YW collected and analyzed data. YH and JX helped with data analysis. ZY helped with data collection. BX and HL wrote the draft. YB revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Assessment of risk scores to predict mortality of COVID-19 patients admitted to the intensive care unit

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Objectives: To assess the ABC_2-SPH score in predicting COVID-19 in-hospital mortality, during intensive care unit (ICU) admission, and to compare its performance with other scores (SOFA, SAPS-3, NEWS2, 4C Mortality Score, SOARS, CURB-65, modified CHA2DS2-VASc, and a novel severity score).

Materials and methods: Consecutive patients (≥ 18 years) with laboratory-confirmed COVID-19 admitted to ICUs of 25 hospitals, located in 17 Brazilian cities, from October 2020 to March 2022, were included. Overall performance of the scores was evaluated using the Brier score. ABC_2-SPH was used as the reference score, and comparisons between ABC_2-SPH and the other scores were performed by using the Bonferroni method of correction. The primary outcome was in-hospital mortality.

Results: ABC_2-SPH had an area under the curve of 0.716 (95% CI 0.693–0.738), significantly higher than CURB-65, SOFA, NEWS2, SOARS, and modified CHA2DS2-VASc scores. There was no statistically significant difference between ABC_2-SPH and SAPS-3, 4C Mortality Score, and the novel severity score.

Conclusion: ABC_2-SPH was superior to other risk scores, but it still did not demonstrate an excellent predictive ability for mortality in critically ill COVID-19 patients. Our results indicate the need to develop a new score, for this subset of patients.

KEYWORDS

SARS-CoV-2, COVID-19, intensive care unit, prognosis, mortality, risk scores

Introduction

Since its breakthrough, the COVID-19 pandemic caused a collapse of healthcare systems around the world, with an exceeding demand for intensive care beds and mechanical ventilators (1, 2). Increasing cases and widespread dissemination of SARS-CoV-2 created the perfect scenario for the acquisition of advantageous mutations, modifying viral transmissibility and disease severity, and allowing escape from natural or vaccine-mediated immunity (3, 4).

In this context, a rapid, objective, and reliable evaluation of critically ill patients is fundamental for efficient triage, as well as for treatment, and resource allocation. Patients with COVID-19 may deteriorate rapidly after a period of reasonably mild symptoms, reinforcing the need for early risk stratification (5, 6).

Our research group has developed the ABC_2-SPH score, which is the only score developed and validated in Brazilian COVID-19 patients. It uses strict methodological criteria, with few, easily obtained clinical and laboratory data at hospital presentation to predict in-hospital mortality. ABC_2-SPH score has shown high accuracy to discriminate between high-risk and non-high-risk patients, superior to several other scores in a large sample of Brazilian patients (7). Nevertheless, this score has not been validated yet to be applied at ICU admission.

Therefore, our aim was to assess the ABC_2-SPH score, during intensive care unit (ICU) admission, in predicting COVID-19 in-hospital mortality, and to compare its performance with other scores: Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score III (SAPS-3), National Early Warning Score 2 (NEWS2), 4C Mortality Score, SOARS, CURB-65, modified CHA2DS2-VASc, and a novel severity score.

Materials and methods

This study is part of the Brazilian COVID-19 Registry, a retrospective multicenter cohort, which included data from 25 hospitals in Brazil, in 17 cities, with a total of 752 ICU beds, described in detail elsewhere (7).

Study subjects

Consecutive patients (aged ≥18 years) with laboratory-confirmed COVID-19 (positive SARS-CoV-2 RT-PCR or rapid antigen test), according to World Health Organization guidance, admitted to the ICUs of one of the participating hospitals, between 4 October 2020, and 13 March 2022, were included. Patients with missing data in any of the variables used for the ABC_2-SPH score, as well as pregnant patients and those who were admitted for other reasons and developed COVID-19 during their hospital stay were not included in this analysis (Figure 1).

Data collection

Demographic information, clinical characteristics, laboratory findings, therapeutic interventions, and outcomes were collected by trained researchers from patient charts to the Research Electronic Data Capture (REDCap) electronic platform, hosted at the Telehealth Center of the *Hospital das Clínicas of Universidade Federal de Minas Gerais (UFMG)* (8–10). For analysis, only the first ICU admission was considered if the patient had two distinct admissions in the same hospital stay.

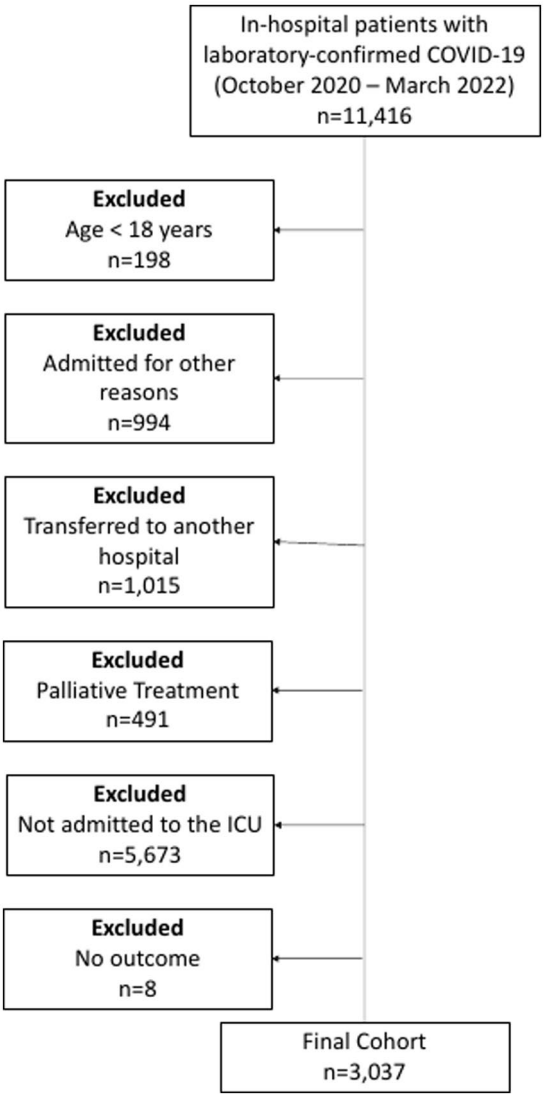

FIGURE 1
Flowchart of COVID-19 patients included in the study.

Periodical data quality checks were performed to ensure data accuracy. Values likely related to data entry errors were identified using a code developed in R software, based on expert-guided rules. Those data were sent to each center for checking and correction (7).

Sample size

Standardized methodology from the Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) checklist (11) recommends that ideally, at least 250 events (in this case, deaths) and 250 non-events should be included for score validation. In the present analysis, there was no formal sample size calculation. Instead, all eligible patients were included, with a sample size that met those requirements.

ABC_2-SPH

The ABC_2-SPH score was developed, validated, and reported following guidance from the TRIPOD checklist (11, 12) and the Prediction model Risk Of Bias Assessment Tool (PROBAST) (13).

The score was derived from a population of 3,978 hospital inpatients, from 36 hospitals, using data upon hospital presentation. Validation was conducted on 1,054 inpatient records from the same institutions (temporal validation) and also on patients from the Vall d'Hebron University Hospital cohort (external validation) (7, 14).

The score incorporates the following variables: **A**ge, **B**UN (blood urea nitrogen), **C**omorbidities, **C**-reactive protein, **S**pO_2/FiO_2 ratio, **P**latelet count, and **H**eart rate. The score ranges from 0 to 20, with risk groups defined as low (0–1), intermediate (2–4), high (5–8), and very high (≥ 9). In the validation cohorts, it has shown high discriminatory ability, with AUROC of 0.859 (95% CI 0.833–0.885) and 0.894 (95% CI 0.870–0.919) for the Brazilian and Spanish cohorts, respectively, and displayed better discrimination ability than other existing scores (7).

Comparison with other risk scores

The accuracy of the ABC_2-SPH score was compared with that of other scores developed specifically for COVID-19. Additionally, we compared the ABC_2-SPH score with scores developed for other conditions, such as pneumonia and sepsis, applied in severely ill or ICU patients and with early warning scores. The scores used for such comparisons were chosen based on two conditions: (1) they had already been evaluated for COVID-19 in other studies, and (2) they used parameters that were available within our database, with accessible methods for calculation (described in a previous publication). They are SOFA (15), SAPS-3 (16, 17), NEWS2 (18), 4C Mortality Score (19, 20), SOARS (21), CURB-65 (22), and a novel severity score developed by Altschul et al. (23). A modified version of the CHA2DS2-VASc score tested in a previous publication to assess mortality in ICU COVID-19 patients (scoring for male sex instead of female) was included in the comparison as well (24). Model comparisons were performed using AUROC and the decision curve analysis.

Outcome

The primary outcome was all-cause in-hospital mortality (considering the entire period of hospitalization).

Statistical analysis

Continuous variables were summarized as medians and interquartile ranges (IQR), and categorical variables as counts and percentages. Data were imputed for variables with up to 30% missing values. This study reported 95% confidence intervals (CI), and a p-value <0.05 was considered statistically significant. Statistical analysis was performed using the free software R (version 4.0.2), and the packages tidyverse, gt, gtsummary, ggplot2, and rms (25).

ABC_2-SPH was used as the reference score for every comparison since it is the only mortality risk score for COVID-19 tested and validated in the Brazilian population (7). Comparisons between ABC_2-SPH and the other scores were performed by the Bonferroni correction method.

Performance measures

The area under the receiver operating characteristic curve (AUROC) described the models' discrimination Confidence intervals for AUROC were obtained across 2,000 bootstrap samples.

Overall performance of the scores was evaluated using the Brier score (26). Only the ABC_2-SPH, SAPS-3, and 4C Mortality scores provided data that allowed calibration. It was performed by plotting the predicted mortality probabilities against the observed mortality, testing intercept equals zero and slope equals one.

We further performed a subgroup analysis comprising the worst phase of the pandemic in Brazil (between 1 March 2021, and 30 April 2021), according to epidemiological data provided by the Brazilian Ministry of Health (27).

Results

A total of 3,037 patients were included, 55.9% were men, with a median age of 61 (IQR 50–70) years old and overall mortality of 50.0%. When comparing patients who died with those who were discharged alive from the hospital, the first group was older and had a higher prevalence of underlying comorbidities such as hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease, and cancer, moreover lower platelet levels, higher urea, and C-reactive protein levels, at ICU admission (Supplementary Table S1).

Table 1 and Figure 2 show the discrimination ability expressed as the AUROC for each of the scores evaluated, while Table 2 depicts the results of the statistical comparison between these scores and ABC_2-SPH, selected as the reference score.

As seen in Table 2, ABC_2-SPH had higher discrimination than CURB65, SOFA, NEWS2, SOARS, and modified CHA2DS2-VASc scores (AUROC: 0.716 [95% CI 0.693–0.738]). There was no statistically significant difference between ABC_2-SPH and SAPS-3, 4C Score, and the novel score by Altschul. Even though the AUROC of SAPS-3 was the second lowest in absolute terms (0.614, 95% CI 0.566–0.663), there was no statistically significant difference between that and the ABC_2-SPH

TABLE 1 Discrimination ability for each score applied in the database of COVID-19 patients admitted to the intensive care unit.

Model	*N**	AUROC (95%CI)
ABC_2-SPH	1,823	0.716 (0.693–0.738)
Altschul et al. (23)	1,334	0.715 (0.688–0.742)
4C Mortality Score	985	0.706 (0.673–0.739)
CURB-65	2,149	0.652 (0.630–0.675)
SOARS	2,515	0.642 (0.621–0.662)
SOFA	928	0.642 (0.601–0.678)
Modified CHA2DS2-VASc	2,787	0.628 (0.608–0.648)
SAPS-3	541	0.614 (0.566–0.663)
NEWS2	1,095	0.605 (0.574–0.637)

*Complete case analysis. Data were imputed for variables with up to 30% missing values.

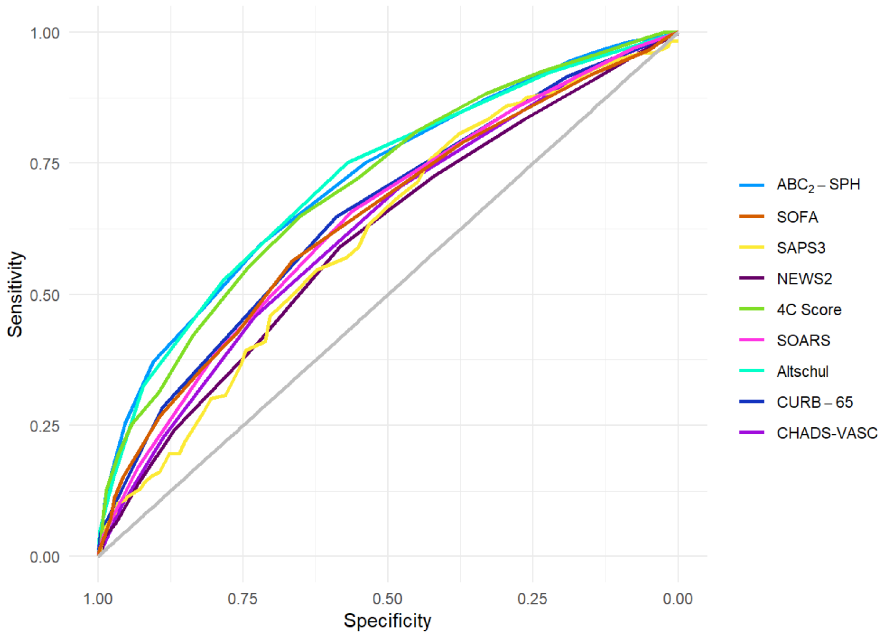

FIGURE 2
Discrimination of ABC_2-SPH and other scores in this cohort.

TABLE 2 Comparison between ABC_2-SPH and other scores.

Reference score	Compared score	*p*-value	alpha*	*N*	Result
ABC_2-SPH	Altschul et al. (23)	0.9346	0.0063	1,094	AUROC of ABC_2-SPH is not different
ABC_2-SPH	4C Mortality Score	0.8878	0.0063	815	AUROC of ABC_2-SPH is not different
ABC_2-SPH	CURB-65	0.0010	0.0063	1,823	AUROC of ABC_2-SPH is larger**
ABC_2-SPH	SOARS	0.0000	0.0063	2,147	AUROC of ABC_2-SPH is larger**
ABC_2-SPH	SOFA	0.0032	0.0063	842	AUROC of ABC_2-SPH is larger**
ABC_2-SPH	Modified CHA2DS2-VASC	0.0000	0.0063	2,380	AUROC of ABC_2-SPH is larger**
ABC_2-SPH	SAPS-3	0.0046	0.0063	539	AUROC of ABC_2-SPH is not different
ABC_2-SPH	NEWS2	0.0000	0.0063	976	AUROC of ABC_2-SPH is larger**

AUROC, area under the ROC curve. *Due to the multiple comparisons, alpha was corrected using Bonferroni method. **ABC_2-SPH has higher discrimination ability.

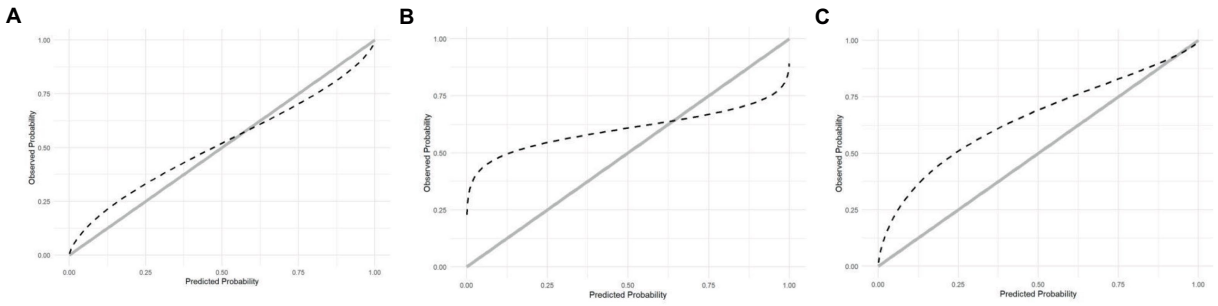

FIGURE 3
(A) Calibration of ABC_2-SPH. **(B)** Calibration of SAPS3. **(C)** Calibration of 4C Score.

score. SAPS-3 had the smallest sample, with only 541 patients included in the analysis, and this might explain the lack of significance.

The calibration curve indicates that the ABC_2-SPH underestimated mortality at lower ranges of the score and overestimated it at the higher ones. In other words, the less severely ill patients have had a worse outcome than the score could predict, as seen in Figure 3A. SAPS-3 had an even greater underestimation of mortality at lower ranges and overestimation at the higher ranges (Figure 3B). The 4C Mortality score, on the other hand, underestimated mortality through all the ranges of the score (Figure 3C). The calibration curves could not be produced for the remaining scores because it was not possible to access their original derivation data.

Discussion

In the present study, ABC_2-SPH presented a reasonable performance when applied during ICU admission in predicting COVID-19 in-hospital mortality, and it was significantly better than CURB-65, SOFA, NEWS2, SOARS, and the modified version of CHA2DS2-VASc. When comparing the performance of the ABC_2-SPH to the SAPS-3, 4C Score, and the score by Altschul et al., we did not observe significant differences.

In the context of the COVID-19 pandemic, many new risk scores were developed and others were tested, or even adapted. A modified version of CHA2DS2-VASc score (giving 1 point for the male sex and 0 points for the female sex, considering male sex a risk factor for COVID-19) was evaluated in 209 intensive care patients, with the rationale that endothelial dysfunction and thrombosis are important components of COVID-19 pathophysiology, but it had fair results (24).

Most of the studies carried out to test or develop risk scores for COVID-19 patients at ICU admission used small samples, increasing the imprecision and compromising the external validity of the results. For instance, a prospective study compared different early warning scores, applied at admission to the ICU, to predict mortality in 140 critically ill patients with laboratory-confirmed COVID-19 (18). The overall performance was intermediate, and the confidence intervals were too wide, conferring significant imprecision to the results. CRB-65, the best discriminatory tool in that study, showed an AUC of 0.720 (95% CI 0.630–0.811).

In a larger study, the performance of SAPS-3 was evaluated in 30,571 COVID-19 patients admitted to ICUs in Brazil. The model's discrimination was excellent, with an AUROC of 0.835 (95% CI 0.828–0.841). However, the mortality was considerably lower than in our cohort (15.0% vs. 50.0%), as well as in other studies with critically ill COVID-19 patients from varied countries, which had a mortality rate between 26 to 50% (28–33). The low mortality rate may have influenced SAPS-3 outperformance in that specific study. Still, the calibration was inappropriate, with an underestimation of mortality in lower to intermediate-risk groups, and an overestimation in the higher-risk group (16).

An Italian group developed and internally validated a prediction model for 28-day mortality of critically ill COVID-19 patients admitted to the ICU. This study used clinical variables (age, obesity,

procalcitonin, SOFA score, and PaO_2/FiO_2 ratio), with an excellent discriminatory capacity of 0.821 (95% CI 0.766–0.876) and 0.822 (95% CI 0.770–0.873), in the original and bootstrap models, respectively (34). Nevertheless, some limitations should be mentioned: the model lacks external validation, the authors included a relatively small sample of participants, and the inclusion of serum procalcitonin (a less available laboratory test) limits the widespread use of this score.

In a multicenter cohort in Italy, a machine learning (ML) approach was applied for the development and validation of a predictive model, utilizing many clinical variables. The performance was better when the variables were collected both at ICU admission and during ICU stay (even though with more than 85% of missing data) and were less satisfactory considering only the variables collected at ICU admission that had less than 85% of missing data (35). The sample was modest for a ML approach, with only 1,293 patients for score development, and less than 100 events in the external validation datasets. Still, there was no information on the imprecision of the results, as the authors did not provide the confidence intervals.

Knight et al. (2020) developed and validated the 4C Mortality Score, which uses eight variables readily available at hospital admission, with reasonable discrimination for mortality (AUC 0.774, CI 95% 0.767–0.782) and excellent calibration. Nevertheless, this score was aimed to be used at the moment of hospital admission, not necessarily at ICU admission, and has not been validated for such use (20).

A multicenter retrospective cohort study carried out in Spain and conducted on patients transferred by ambulance to an emergency department evaluated the NEWS2 performance. The NEWS2 score provided an AUROC ranging from 0.825 for 1-day mortality to 0.777 for 90-day mortality. Nevertheless, the hospitalization rate of the 2,961 patients included was 78.6%, while patients that required ICU admission represented only 5.5% of the total participants, and no subgroup analysis was made (36).

The validation of the ABC_2-SPH in a large cohort of patients admitted to ICU due to COVID-19 complications could be helpful, given that other scores proved to be inaccurate in this scenario. Nevertheless, despite its excellent discrimination for mortality at hospital admission, the results were only reasonable when applied at ICU admission. The AUROC of 0.716 (95% CI 0.693–0.738) was considerably inferior to that observed in the original study (7). The same happened with the widely used SAPS-3, SOFA, and NEWS2, as described above, which had a worse performance than ABC_2-SPH.

We initially hypothesized that one of the reasons that could explain such unsatisfactory performances is that our cohort was composed exclusively of patients from Brazilian hospitals, including patients admitted during the worst wave of the pandemic in Brazil (27). This could have affected the performance of the scores, since the collapse of the health system may have led many patients to be admitted to ICUs at late phases of the disease, making their recovery more difficult. Another possibility could be that, under the huge saturations of the ICUs during the worst waves, the most critically ill patients did not get admitted into the ICU, with the ones with a better prognosis getting the priority. Nevertheless, in a subgroup analysis of the patients evaluated during the worst phase of the pandemic in Brazil, between 1 March 2021 and 30 April 2021, there was no significant difference in the performance of ABC_2-SPH (Supplementary Table S2).

Some aspects of each score may have had a negative impact on their performance in this study. ABC_2-SPH, for instance, uses the SF ratio (SpO_2/FiO_2) as one of its parameters: the lower the ratio, the higher the score, indicating a higher probability of death. Nevertheless, patients admitted to the ICU are frequently on mechanical ventilation (38.1% of all patients evaluated, being 49.1% among those who died and 27.3% among the survivors), which may lead to an inadequate degree of hyperoxia, not necessarily a less severe clinical state, and this could potentially mislead the score.

Besides that, of all the parameters included in ABC_2-SPH, involving different organ systems, only the SF ratio is directly related to the respiratory system, which is the main cause of death in COVID-19 patients (37). Perhaps, the inclusion of more parameters related to the respiratory system, such as the severity of lung involvement in computerized tomography, could improve the accuracy of the score. The use of imaging methods might cause some mistrust, being it operator-dependent, but the development of machine-learning techniques could eventually surpass this issue.

On the other hand, SOFA includes the mean arterial pressure as one of its parameters, giving it the same value as PaO_2/FiO_2 ratio for the score (0 to 4 points). Nevertheless, unlike respiratory impairment, hypotension does not seem to be part of the main core of COVID-19 mortality, in the absence of a specific cause.

Likewise, SAPS-3 uses many different parameters which might not be as relevant for COVID-19 mortality. Age just above 40 years already scores 5 points, enough to almost double the probability of death. In contrast, according to our database, the risk of death in the age group of 40–49 years old is 33.5%, compared to 25.6% of those aged 18–29 years old. The risk of death, in reality, only doubles in the age group of 60–69 years old (54.1%) (Supplementary Table S3). Furthermore, SAPS-3 includes a large number of variables that do not apply to our set of patients, such as the reason for ICU admission (in this study, admission for some reason other than COVID-19 was an exclusion criterion). And the same way that SOFA, mean arterial pressure is as valued as PaO_2/FiO_2 ratio.

Therefore, we hypothesized that such imbalances between clinical importance and the weight of each variable included in the scores could be a reason for such unsatisfactory performances.

This study has limitations that deserve comments. Hospitals from different regional settings and different sizes were included in the study to increase external validity. However, infrastructure unbalances between them may have impacted the results. In addition, some of the scores ended up with fewer participants than others due to incomplete data, since data were imputed for variables with up to 30% missing values. SAPS-3, as mentioned above, is an example of that. Furthermore, the scores chosen to be included in the analysis were limited to the parameters available within our database, leaving some others out of the study.

Further and periodical adjustments, in a similar manner that happens with other risk scores which are subjected to continuous updates (such as APACHE and SAPS), should also be considered for ABC_2-SPH.

Conclusion

In this study, applying ABC_2-SPH at ICU admission had a reasonable performance in predicting in-hospital mortality of COVID-19 critically ill patients, superior to other risk scores. In order

to obtain excellent performance, nevertheless, it may be necessary to develop a new score for this specific subset of patients.

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 study protocol was approved by the Brazilian National Commission for Research Ethics (CAAE: 30350820.5.1001.0008) on April 2, 2020, with the following title (free translation): "Evaluation of the laboratory, radiological and symptomatological profile of infected patients with the new coronavirus 2019 (SARS-CoV-2) in hospitals in the State of Minas Gerais." The study title has been changed on 10 June 2020 to "National multicenter hospital registry of patients with disease caused by SARS-COV-2 [COVID-19]," also in free translation. Individual informed consent was waived by a regulatory board due to the severity of the situation and the use of deidentified data, based on medical chart review only. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies and it is in accordance with the Declaration of Helsinki.

Author contributions

MSM, VN, MCP, LEFR, and YCNMBR: conception or design of the work. MCAN, VN, MCP, LEFR, YCNMBR, RLOA, FMBV, VMRG, COS, DMM, PAAD, JMC, AVS, AGRG, BPP, CCM, CCRC, CAC, DP, ERFM, EPAC, FA, FCCC, FJMN, FB, GMSG, HRV, JCN, KBR, LBZ, LCC, MDS, MC, MACB, MNV, NPFB, NRO, RL, SCF, SFA, PDP, and MSM: acquisition, analysis, or interpretation of data for the work. MCAN, VN, PDP, and MSM: drafted the work. MSM and MCAN agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors were revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Telephone triage service use is associated with better outcomes among patients with cerebrovascular diseases: a propensity score analysis using population-based data

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Introduction: The telephone triage service is an emergency medical system through which citizens consult telephone triage nurses regarding illness, and the nurses determine the urgency and need for an ambulance. Despite being introduced in several countries, its impact on emergency patients has not been reported. We aimed to determine the effect of the telephone triage service on the outcomes of hospitalized patients diagnosed with cerebrovascular disease upon arrival after being transported by an ambulance.

Methods: This retrospective study included patients with cerebrovascular disease who were transported by ambulance between January 2016 and December 2019. The primary outcome was discharge to home by day 21 of hospitalization. A total of 344 patients who used the telephone triage service were propensity score-matched to 344 patients who directly called for an ambulance.

Results: Telephone triage service use was associated with discharge to home by hospital day 21 (crude odd ratio: 1.8; 95% confidence interval: 1.3–2.4) and was not significantly associated with survival on hospital day 21 in multivariate regression analysis.

Conclusion: The prognoses of cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage depend on the time from symptom onset to treatment. Telephone triage services may allow patients to receive treatment more rapidly than traditional ambulance requests, resulting in improved patient outcomes. The findings of this study suggest that the use of telephone triage services is associated with improved outcomes in patients with cerebrovascular disease and indicate that the costs for medical expenses and disability may be greatly reduced in an aging society.

KEYWORDS

telephone triage service, cerebrovascular disease, acute stroke, triage protocol, propensity score-matched analysis

1. Introduction

Telephone triage services help in the provision of necessary emergency medical services to patients by enabling an evaluation of the patients' conditions over the telephone. Using information provided by the patient, nurses assess the patient's condition and can dispatch an ambulance, suggest appropriate hospitals, or send a visiting physician. This necessary service has been introduced in several countries, including the United Kingdom and Australia (1, 2). In Japan, telephone triage services were introduced in Tokyo in 2007 and in Osaka in 2009 (3). A previous study reported that the telephone triage service in the Osaka Prefecture effectively triaged patients, dispatched ambulances, and suggested appropriate medical institutions (4). The annual number of emergency medical consultations in Osaka Prefecture was mostly more than 100,000 (5).

Patients who are deemed as emergency cases based on telephone triage services should be admitted directly to the emergency department upon arrival by ambulance (2). The relationship between the use of telephone triage services and patient outcomes is unclear, though the use of telephone triage services is associated with a lower proportion of unfavorable patient outcomes (6, 7). In addition, it remains unclear what diseases it is especially effective for (6, 8).

As telephone triage services encourage patients to visit a hospital immediately by performing emergency triage according to a protocol, it may be more effective for patients with cerebrovascular diseases than for patients with other diseases, since the time from symptom onset to treatment significantly affects the prognosis of patients with cerebrovascular diseases. However, whether telephone triage services are effective for patients with cerebrovascular diseases remains unclear. If these services positively affect the prognoses of these patients, their use may become more widespread, which would further improve patient outcomes.

Using propensity score matching, this study evaluated the effects of a telephone triage service on the outcomes of patients with cerebrovascular diseases who were transported by ambulance and hospitalized.

2. Methods

2.1. Study design

This retrospective study included hospitalized patients with cerebrovascular diseases (International Classification of Diseases 10th edition [ICD-10] code: I60.0-I69.8) transported by the Osaka Municipal Fire Department (OMFD) between January 1, 2016, and December 31, 2019. Patients who were transported in the same ambulance with other patients and those with missing data were excluded from the analysis. Anonymized data from the Osaka Emergency Information Research Intelligent Operation Network system (ORION), published in 2022, were used in this study (7). This manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology statement to assess the reporting of cohort and cross-sectional studies (9).

2.2. Study area

Osaka City is the largest metropolitan area in western Japan (225.33 km^2), with a population of approximately 2.75 million people (10). A total of 94 medical institutions receives ambulances in Osaka City, and the total number of ambulance dispatches by the OMFD during the study period was 942,778 (11).

2.3. Telephone triage service in Osaka City

The telephone triage service in Osaka City has been described previously (4). In summary, a telephone triage nurse assesses the urgency of a caller's symptoms using only the telephone triage protocol for each chief complaint (4). In principle, the emergency assessment in this service does not require doctors and is not affected by patients' requests. This telephone triage service is similar to those in the United States, Canada, and the United Kingdom (1, 12, 13). Telephone triage services and ambulance requests in Japan are public services that are free of charge. Based on patient assessments, telephone triage nurses can dispatch an ambulance or suggest an appropriate medical institution (14). The Japanese telephone triage protocol includes 98 chief complaints for adults and children, and patients are triaged according to the signs and symptoms related to the chief complaints (14). In addition, data regarding telephone triage, such as sex, patient age, time of call initiation, end time of call, chief complaint, signs, urgency assessment, and whether an ambulance was dispatched or not, are recorded using the software. During the study period, 466,744 emergency medical consultations were conducted in the Osaka prefecture, including 20,387 ambulance dispatches requested by the telephone triage nurses (14).

2.4. Ethical consideration

This study was approved by the Institutional Review Board of Osaka Metropolitan University Hospital (approval number: 2021–233). As we used anonymized data provided by the OMFD, the requirement of obtaining patients' informed consent was waived.

2.5. Main outcome

We defined the primary outcome of this study as the proportion of patients diagnosed with cerebrovascular disease upon arrival at the hospital by ambulance who were discharged to home on hospital day 21 (15). We wanted to consider neurological assessment as an outcome of cerebrovascular disease, but we did not have the relevant assessment information (such as Glasgow Outcome Scale and modified Rankin Scale). We assumed that home discharge outcomes were correlated with better neurological outcomes. That's why we used discharge to home as the primary outcome. The secondary outcome was defined as survival on hospital day 21 in patients diagnosed with cerebrovascular disease upon arrival at the hospital by ambulance.

2.6. Propensity score matching

Patient propensity scores were calculated using a logistic regression model with nine variables that existed before the use of the telephone triage service or were indicative of the patient's condition, including age, sex, calendar year, season, time, holiday (including weekends), accident location, consciousness, and administrative

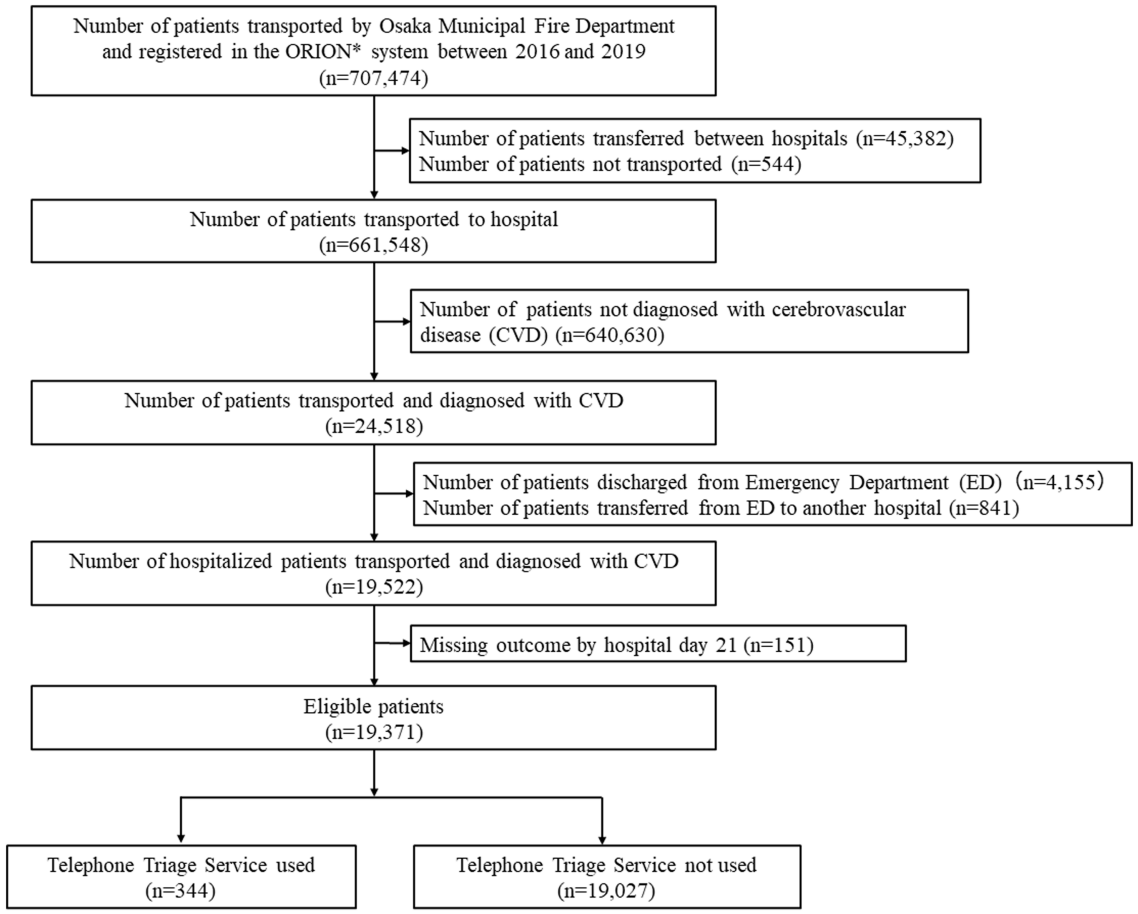

FIGURE 1
Patient flowchart in this study. Between 2016 and 2019, 707,474 patients were transported to medical institutions by Osaka Municipal Fire Department ambulances and were registered in the ORION system. A total of 45,382 patients who were transferred between hospitals and 544 patients who were not transported were excluded. Of the remaining patients, 24,518 had a diagnosis of cerebrovascular disease upon arrival at the hospital. To evaluate the inpatients' outcomes, 4,155 patients who were discharged from the emergency department (including those who died), 841 patients who were transferred to another hospital, and 151 patients with missing data regarding hospital stay at day 21 were excluded. Ultimately, 19,371 patients were included in this study. Of these patients, 344 (1.8%) had used the telephone triage service and 19,027 (98.2%) had not. *ORION, Osaka Emergency Information Research Intelligent Operation Network.

districts. Seasons were defined as spring from April to June, summer from July to September, autumn from October to December, and winter from January to March. The time was considered daytime from 09:00 to 17:59 and nighttime from 18:00 to 08:59. The accident locations were categorized as residences or elsewhere. Consciousness was classified using the Glasgow Coma Scale (GCS) (16) in the ambulance: severe impairment, 3–8 points; moderate impairment, 9–11 points; mild impairment, 12–13 points; and clear, 14–15 points. Administrative districts were classified into 24 areas as defined by Osaka City (17).

The effects of telephone triage service use on patient outcomes were evaluated. One-to-one pair matching was conducted by nearest-neighbor matching without replacement between patients for whom an ambulance was dispatched by the telephone triage service and for those whom an ambulance was dispatched without telephone triage, using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Covariate balances before and after matching were confirmed by comparing the standardized mean differences (SMD). An SMD < 10% was considered as a negligible imbalance between the two groups.

2.7. Statistical analysis

Propensity score matching, univariate and multiple logistic regression models, and regression models with propensity scores as covariates were conducted. The variables used in the calculation of the propensity score and telephone triage services were used in the multiple regression model (Forced entry method). All statistical analyses were performed using SPSS version 25.0 J (IBM Corp. Armonk, NY, United States). All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$.

3. Results

Between 2016 and 2019, 707,474 patients were transported to medical institutions by OMFD ambulances and were registered in the ORION system (Figure 1). A total of 45,382 patients who were transferred between hospitals and 544 patients who were not transported were excluded from the study. Of the remaining patients, 24,518 had a diagnosis of cerebrovascular disease upon arrival at the

hospital. To evaluate the inpatients' outcomes, 4,155 patients who were discharged from the emergency department (including those who died), 841 patients who were transferred to another hospital, and 151 patients with missing data regarding hospital day 21 were excluded. Ultimately, 19,371 patients were included in this study. Of these patients, 344 (1.8%) had used the telephone triage service and 19,027 (98.2%) had not. Patients who used telephone triage services were younger and had a milder impairment of consciousness than those who did not (Table 1).

Approximately 90% of telephone triage service users were located at their residences. A total of 344 patients from the group that did not use the telephone triage service were matched to those who used the service using propensity score matching, and the balance of each covariate improved between the two groups after propensity score matching. The area under the curve in the logistic regression model for propensity score calculation was 0.746.

The most common cerebrovascular events diagnosed among all patients were cerebral infarction (59.5%, 11,520 patients), intracerebral hemorrhage (25.2%, 4,880 patients), and subarachnoid hemorrhage (6.2%, 1,209 patients) (Table 2). Of the 19,371 patients included in this study, 7,551 (39.0%) were discharged home by hospital day 21, including 199 (57.8%) patients who used the telephone triage service and 7,352 (38.6%) patients who did not use the telephone triage service. Telephone triage service use was associated with discharge to home by hospital day 21 (crude odds ratio [OR]: 2.2; 95% confidence interval [CI]: 1.8–2.7), and was also independently associated with discharge to home by hospital day 21 (adjusted OR: 1.8; 95% CI: 1.5–2.3). This association was also observed in the propensity score-matched analysis (crude OR: 1.8; 95% CI: 1.3–2.4) (Table 3), when the propensity score was included as a covariate (adjusted OR: 1.8 95% CI: 1.4–2.2).

Of the 19,371 patients included in this study, 18,325 (94.6%) survived on hospital day 21, including 340 (98.8%) patients who used the telephone triage service and 17,985 (94.5%) patients who did not. Telephone triage service use was associated with survival on hospital day 21 by univariate regression model analysis (crude odds ratio (OR): 4.9; 95% confidence interval (CI): 1.8–13.2). However, telephone triage service use was not associated with survival on hospital day 21 by multivariate regression model analysis (adjusted OR: 2.4; 95% CI: 0.9–6.7). This association was also not observed when the propensity score was included as a covariate (adjusted OR: 2.0; 95% CI: 0.6–6.8) in the propensity score-matched analysis (crude OR: 2.0; 95% CI: 0.6–6.8) (Table 4).

4. Discussion

The effects of telephone triage services on emergency care for cerebrovascular diseases in the urban areas of Japan were evaluated in this study. The most common cerebrovascular diagnosis was cerebral infarction, followed by intracerebral hemorrhage and subarachnoid hemorrhage. Among patients hospitalized with cerebrovascular diseases, telephone triage service use was associated with discharge to home by hospital day 21, which meant this service might be associated with improved neurological outcome (18). No significant associations were found between using this service and patient survival.

Previous studies have not reported the diagnoses of the patients who used telephone triage services. Therefore, it remained unclear what diseases the telephone triage service was effective for. The ORION system data includes ICD-10 coded diagnoses of patients transported by ambulance. In this study, the positive effects of telephone triage services on the outcomes of patients with cerebrovascular diseases were clarified. The prognoses of cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage are dependent on the time from symptom onset to treatment (19–21). Some treatments for these conditions cannot be implemented after a specific number of hours have passed from the time of symptom onset (22). Telephone triage service nurses may allow patients to receive treatment more rapidly than traditional ambulance requests, which may result in improved patient outcomes and lower medical and social security costs. While these findings may be applied worldwide, health care systems and ambulance request fees vary in different countries, which may affect the use and cost of telephone triage services.

The American Heart Association (AHA) describes the process from the onset of stroke to hospitalization as the 'Ds' of stroke care (23). The use of telephone triage services may shorten the detection (rapid recognition of stroke symptoms), dispatch (early activation and dispatch of emergency medical services system by calling 9–1-1), and delivery (rapid emergency medical service identification, management, and transport) processes described by the AHA. Citizens may choose to use telephone triage services that are free to the public over direct ambulance dispatch services due to the high costs associated with such services. The telephone triage service in the Osaka Prefecture used the face, arm, speech, time (FAST) acronym when triaging patients with stroke, which may have resulted in rapid and accurate ambulance dispatches. The FAST acronym is a simple screening algorithm created based on the Cincinnati Prehospital Stroke Scale (24). The algorithm identifies 88.9% of patients with stroke or transient ischemic attack and 99.9% of patients at acute onset (25). The use of telephone triage services may also shorten the time required to identify appropriate hospitals, improving the transportation process. Acute stroke is associated with a high risk of death and severe complications and requires long-term hospitalization, especially in older adults (26), and cerebral infarction is the most common disease among all hospitalized patients who arrive by ambulance (4). The findings of this study suggest that the use of telephone triage services is associated with improved outcomes in patients with cerebrovascular disease and indicates that the costs for medical expenses and disability may be greatly reduced in an aging society.

This study has several limitations. First, this study tended to include patients with mild cerebrovascular diseases. It remains unclear whether telephone triage will be useful for all severities of cerebrovascular diseases in ambulance transports. Telephone triage services may be unsuitable for patients with severe cerebrovascular diseases because it is reasonable to call an ambulance directly in such cases. Second, the outcomes of cases for which no ambulance was dispatched remain unknown. In the future, we plan to examine patients with cerebrovascular diseases for whom an ambulance was not called because of the telephone triage assessments. Third, we could not collect information related to cerebrovascular disease in this research, such as past medical history, or oral medication history. Fourth, the primary outcome of this study was discharge to home, which predicted the patients' neurological outcomes, although it was affected by environmental factors including economic factors, such as income, and social factors, such as family composition. We were not

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TABLE 1 Patient characteristics before and after propensity score matching.

	Telephone triage service used		Telephone triage service not used		SMD**	Telephone triage service used		Telephone triage service not used		SMD
	(*n* =344)		(*n* =19,027)			(*n* =344)		(*n* =344)		
Age (years)										
Mean (SD)	68.8	(13.9)	72.4	(13.8)	0.258	68.8	(13.9)	69.1	(14.2)	0.015
Sex										
Male	200	(58.1%)	11,026	(57.9%)	0.004	200	(58.1%)	208	(60.5%)	0.047
Female	144	(41.9%)	8,001	(42.1%)	0.004	144	(41.9%)	136	(39.5%)	0.047
Consciousness										
Severe impairment (GCS* 3–8 points)	10	(2.9%)	2,203	(11.6%)	0.339	10	(2.9%)	5	(1.5%)	0.100
Moderate impairment (GCS 9–11 points)	13	(3.8%)	2,150	(11.3%)	0.288	13	(3.8%)	20	(5.8%)	0.095
Mild impairment (GCS 12–13 points)	15	(4.4%)	1,432	(7.5%)	0.134	15	(4.4%)	13	(3.8%)	0.029
Clear (GCS 14–15 points)	306	(89.0%)	13,242	(69.6%)	0.492	306	(89.0%)	306	(89.0%)	0.000
Calendar Year										
2016	86	(25.0%)	4,592	(24.1%)	0.020	86	(25.0%)	93	(27.0%)	0.046
2017	94	(27.3%)	4,744	(24.9%)	0.054	94	(27.3%)	100	(29.1%)	0.039
2018	76	(22.1%)	4,832	(25.4%)	0.078	76	(22.1%)	76	(22.1%)	0.000
2019	88	(25.6%)	4,859	(25.5%)	0.001	88	(25.6%)	75	(21.8%)	0.089
Season										
Spring (from April to June)	79	(23.0%)	4,579	(24.1%)	0.026	79	(23.0%)	82	(23.8%)	0.021
Summer (from July to September)	86	(25.0%)	4,412	(23.2%)	0.042	86	(25.0%)	93	(27.0%)	0.046
Autumn (from October to December)	82	(23.8%)	5,088	(26.7%)	0.067	82	(23.8%)	75	(21.8%)	0.049
Winter (from January to March)	97	(28.2%)	4,948	(26.0%)	0.049	97	(28.2%)	94	(27.3%)	0.019
Time										
Daytime (9:00–17:59)	140	(40.7%)	10,235	(53.8%)	0.265	140	(40.7%)	135	(39.2%)	0.030
Nighttime (18:00–23:59, 0:00–8:59)	204	(59.3%)	8,792	(46.2%)	0.265	204	(59.3%)	209	(60.8%)	0.030
Day										
Weekday	189	(54.9%)	12,999	(68.3%)	0.278	189	(54.9%)	201	(58.4%)	0.070
Holiday including weekends	155	(45.1%)	6,028	(31.7%)	0.278	155	(45.1%)	143	(41.6%)	0.070
Accident location										
Residence	302	(87.8%)	11,955	(62.8%)	0.605	302	(87.8%)	305	(88.7%)	0.027
Elsewhere	42	(12.2%)	7,072	(37.2%)	0.605	42	(12.2%)	39	(11.3%)	0.027
Administrative district										
Kita-ku	14	(4.1%)	1,072	(5.6%)	0.073	14	(4.1%)	13	(3.8%)	0.015
Miyakojima-ku	19	(5.5%)	726	(3.8%)	0.081	19	(5.5%)	24	(7.0%)	0.060
Fukushima-ku	9	(2.6%)	404	(2.1%)	0.032	9	(2.6%)	9	(2.6%)	0.000
Konohana-ku	6	(1.7%)	494	(2.6%)	0.059	6	(1.7%)	9	(2.6%)	0.060
Chuo-ku	13	(3.8%)	970	(5.1%)	0.064	13	(3.8%)	17	(4.9%)	0.057
Nishi-ku	12	(3.5%)	457	(2.4%)	0.064	12	(3.5%)	11	(3.2%)	0.016
Minato-ku	15	(4.4%)	602	(3.2%)	0.063	15	(4.4%)	16	(4.7%)	0.014
Taisho-ku	7	(2.0%)	568	(3.0%)	0.061	7	(2.0%)	9	(2.6%)	0.039
Tennnoji-ku	13	(3.8%)	479	(2.5%)	0.072	13	(3.8%)	9	(2.6%)	0.066
Naniwa-ku	7	(2.0%)	511	(2.7%)	0.043	7	(2.0%)	8	(2.3%)	0.020
Nishiyodogawa-ku	13	(3.8%)	521	(2.7%)	0.059	13	(3.8%)	15	(4.4%)	0.029
Yodogawa-ku	15	(4.4%)	1,075	(5.7%)	0.059	15	(4.4%)	12	(3.5%)	0.045
Higashiyodogawa-ku	20	(5.8%)	1,112	(5.8%)	0.001	20	(5.8%)	16	(4.7%)	0.052
Higashinari-ku	19	(5.5%)	555	(2.9%)	0.130	19	(5.5%)	15	(4.4%)	0.054
Ikuno-ku	17	(4.9%)	955	(5.0%)	0.004	17	(4.9%)	15	(4.4%)	0.028
Asahi-ku	16	(4.7%)	627	(3.3%)	0.069	16	(4.7%)	13	(3.8%)	0.043
Joto-ku	14	(4.1%)	953	(5.0%)	0.045	14	(4.1%)	18	(5.2%)	0.055
Tsurumi-ku	9	(2.6%)	676	(3.6%)	0.054	9	(2.6%)	9	(2.6%)	0.000
Abeno-ku	13	(3.8%)	671	(3.5%)	0.013	13	(3.8%)	8	(2.3%)	0.085
Suminoe-ku	14	(4.1%)	869	(4.6%)	0.024	14	(4.1%)	13	(3.8%)	0.015
Sumiyoshi-ku	14	(4.1%)	983	(5.2%)	0.052	14	(4.1%)	16	(4.7%)	0.028
Higasisumiyoshi-ku	24	(7.0%)	948	(5.0%)	0.084	24	(7.0%)	26	(7.6%)	0.022
Hirano-ku	29	(8.4%)	1,353	(7.1%)	0.049	29	(8.4%)	31	(9.0%)	0.021
Nishinari-ku	12	(3.5%)	1,446	(7.6%)	0.180	12	(3.5%)	12	(3.5%)	0.000

GCS*, Glasgow Coma Scale; SMD**, Standardized Mean Differences.

TABLE 2 Number of hospitalized patients with cerebrovascular diseases transported by ambulance in this study.

Diagnosis by ICD-10 code	Total (*n* =19,371)		Telephone triage service used (*n* =344)		Telephone triage service not used (*n* =19,027)	
I60. Subarachnoid hemorrhage	1,209	(6.2%)	9	(2.6%)	1,200	(6.3%)
I61. Intracerebral hemorrhage	4,880	(25.2%)	55	(16.0%)	4,825	(25.4%)
I62. Other nontraumatic intracranial hemorrhage	698	(3.6%)	11	(3.2%)	687	(3.6%)
I63. Cerebral infarction	11,520	(59.5%)	254	(73.8%)	11,266	(59.2%)
I64. Stroke, not specified as hemorrhage or infarction	126	(0.7%)	1	(0.3%)	125	(0.7%)
I65. Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	114	(0.6%)	2	(0.6%)	112	(0.6%)
I66. Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	141	(0.7%)	1	(0.3%)	140	(0.7%)
I67. Other cerebrovascular diseases	366	(1.9%)	5	(1.5%)	361	(1.9%)
I68. Cerebrovascular disorders in diseases classified elsewhere	12	(0.1%)	0	(0.0%)	12	(0.1%)
I69. Sequelae of cerebrovascular disease	305	(1.6%)	6	(1.7%)	299	(1.6%)

TABLE 3 Discharge to home of hospitalized patients with cerebrovascular diseases transported by ambulance.

	Total		Telephone triage service used		Telephone triage service not used		Crude OR	(95% CI)	Adjusted OR	(95% CI)	*p* value
All patients	(*n* = 19,371)		(*n* = 344)		(*n* = 19,027)						
Discharge to home by hospital day 21	7,551	(39.0%)	199	(57.8%)	7,352	(38.6%)					
Univariate logistic regression model							2.2	(1.8–2.7)	–	–	<0.01
Multivariate logistic regression model*							–	-	1.8	(1.5–2.3)	<0.01
Regression model with propensity score as covariate							–	–	1.8	(1.4–2.2)	<0.01
Propensity score-matched patients	(*n* = 688)		(*n* = 344)		(*n* = 344)						
Discharge to home by hospital day 21	349	(50.7%)	199	(57.8%)	150	(43.6%)	1.8	(1.3–2.4)	–	–	<0.01

OR, odds ratio; CI, confidence interval. ORs were calculated for patients with versus without telephone triage service. *Adjusted for age, sex, calendar year, season, time, holiday including weekends, accident location, consciousness, and administrative district.

TABLE 4 Survival of hospitalized patients with cerebrovascular diseases transported by ambulance.

	Total		Telephone triage service used		Telephone triage service not used		Crude OR	(95% CI)	Adjusted OR	(95% CI)	*p* value
All patients	(*n* = 19,371)		(*n* = 344)		(*n* = 19,027)						
Survival on hospital day 21	18,325	(94.6%)	340	(98.8%)	17,985	(94.5%)					
Univariate logistic regression model							4.9	(1.8–13.2)	–	–	<0.01
Multivariate logistic regression model*							–	–	2.4	(0.9–6.7)	0.09
Regression model with propensity score as covariate							–	–	2.0	(0.6–6.8)	0.27
Propensity score-matched patients	(*n* = 688)		(*n* = 344)		(*n* = 344)						
Survival on hospital day 21	676	(98.3%)	340	(98.8%)	336	(97.7%)	2.0	(0.6–6.8)	–	–	0.38

OR, odds ratio; CI, confidence interval. ORs were calculated for patients with versus without telephone triage service. *Adjusted for age, sex, calendar year, season, time, holiday including weekends, accident location, consciousness, and administrative district.

able to adjust for these factors in this study; however, previous studies have shown that regional differences affect the outcomes of patients transported by ambulances (27), and we adjusted for this by including region-related factors as variables in the propensity score analysis. Finally, as this was an observational study, there are likely unknown confounding factors.

5. Conclusion

The use of telephone triage services is associated with improved outcomes among patients with cerebrovascular disease who are transported to hospitals by ambulance. These improved outcomes will likely reduce medical costs in an aging society.

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 This study was approved by the Institutional Review Board of Osaka Metropolitan University Hospital (approval number: 2021–233). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YK and TS conceived the idea of this study. ST and JT contributed to the data collection. RD, HH, YN, and YK contributed to the data analysis and interpretation. RD was a major contributor in writing the manuscript. YK, TN, TK, TS, and YM supervised the conduct of this study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Occurrence of SARS-CoV-2 viremia is associated with genetic variants of genes related to COVID-19 pathogenesis

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Introduction: SARS-CoV-2 viral load has been related to COVID-19 severity. The main aim of this study was to evaluate the relationship between SARS-CoV-2 viremia and SNPs in genes previously studied by our group as predictors of COVID-19 severity.

Materials and methods: Retrospective observational study including 340 patients hospitalized for COVID-19 in the University Hospital La Princesa between March 2020 and December 2021, with at least one viremia determination. Positive viremia was considered when viral load was above the quantifiable threshold (20 copies/ml). A total of 38 SNPs were genotyped. To study their association with viremia a multivariate logistic regression was performed.

Results: The mean age of the studied population was 64.5 years (SD 16.6), 60.9% patients were male and 79.4% white non-Hispanic. Only 126 patients (37.1%) had at least one positive viremia. After adjustment by confounders, the presence of the minor alleles of rs2071746 (*HMOX1*; T/T genotype OR 9.9 $p < 0.0001$), rs78958998 (probably associated with *SERPING1* expression; A/T genotype OR

2.3, $p = 0.04$ and T/T genotype OR 12.9, $p < 0.0001$), and rs713400 (eQTL for *TMPRSS2*; C/T + T/T genotype OR 1.86, $p = 0.10$) were associated with higher risk of viremia, whereas the minor alleles of rs11052877 (*CD69*; A/G genotype OR 0.5, p = 0.04 and G/G genotype OR 0.3, $p = 0.01$), rs2660 (*OAS1*; A/G genotype OR 0.6, $p = 0.08$), rs896 (*VIPR1*; T/T genotype OR 0.4, $p = 0.02$) and rs33980500 (*TRAF3IP2*; C/T + T/T genotype OR 0.3, $p = 0.01$) were associated with lower risk of viremia.

Conclusion: Genetic variants in *HMOX1* (rs2071746), *SERPING1* (rs78958998), *TMPRSS2* (rs713400), *CD69* (rs11052877), *TRAF3IP2* (rs33980500), *OAS1* (rs2660) and *VIPR1* (rs896) could explain heterogeneity in SARS-CoV-2 viremia in our population.

KEYWORDS

SARS-CoV-2, viremia, COVID-19, single nucleotide polymorphism (SNPs), genetic variants

1. Introduction

Almost three years after the SARS-CoV-2 pandemic outbreak, nearly 780 million people have been infected and 65% of the worldwide population has been fully vaccinated against COVID-19. Despite this fact, SARS-CoV-2 circulation seems to persist worldwide and still 1,500 people die every week due to COVID-19 (1). The wide spectrum of clinical manifestations of the disease has encouraged scientists to keep studying different biomarkers that could help us to achieve an early stratification of those patients at higher risk of respiratory impairment and death. In this regard, many clinical conditions and biomarkers such as age, hypertension, Interleukin-6 (IL-6) or D-dimer are associated with COVID-19 severity (2, 3) but the prediction of the clinical course and the pre-existing conditions that confer increased risk, remain a challenge for physicians.

In this sense, SARS-CoV-2 RNA detection in peripheral blood (viremia) has been proposed as a risk factor for severe COVID-19. In previous studies of our group, we have shown that patients with SARS-CoV-2 viremia were more likely to die or be admitted to the Intensive Care Unit (ICU) (4, 5). Other studies (6–8), including a meta-analysis (9) have confirmed these findings correlating SARS-CoV-2 viremia with worse COVID-19 prognosis. Viremia is associated with an increase in the inflammatory response, with higher levels of C-reactive protein or IL-6, as described by Hagman et al. (10) and Myhre et al. (11). In a proteomic study Li et al., evaluated pathways related to the development of viremia and found that patients with viremia had higher expression of SARS-CoV-2 entry factors (ACE2, CTSL, FURIN), proinflammatory markers (such as IL6) as well as markers of tissue damage and coagulation (12). Nevertheless, the mechanisms and predisposing factors, such as genetic factors, leading to viremia are not clear yet.

Several studies have assessed the association between genetic variants and COVID-19 prognosis by Single Nucleotide Polymorphism (SNP) genotyping and Genome-Wide Association Studies (GWAS). Two of the most studied genes are *ACE2* and *TMPRSS2*, involved in SARS-CoV-2 entry, and some of their genetic variants have been associated with COVID-19 severity and infectivity (13–16). Moreover, other regions of genetic susceptibility for COVID-19 severity have been described, such as those related to the ABO blood group system or the antiviral response (OAS1, OAS2, OAS3, TYK2, IFNAR2 or IL-10) (17–19). The review by Anastassopoulou et al. described how disease severity is determined by variants of genes involved in the immune response to the virus, while susceptibility to infection is mainly related to genes that participate in the early stages of infection (such as virus binding and entry) (20). Although these variants could potentially lead to increased entry and dissemination of the virus into the bloodstream, to date no study has addressed the relationship between genetic variants of genes involved in COVID-19 pathogenesis and the detection of viremia.

The main aim of this study was to evaluate the relationship between SARS-CoV-2 viremia and several SNPs in genes previously studied by our group as predictors of COVID-19 severity (13).

2. Materials and methods

2.1. Study design, population and data collection

This is a subanalysis of two previous studies assessing the relationship between different genetic variants related to the pathogenesis of SARS-CoV-2 and COVID-19 severity (13). Both were retrospective observational studies including patients attended at the University Hospital La Princesa (Madrid).

The first study (hereafter study A) recruited 817 patients from the first months of the pandemic (March 29th – April 29th 2020) and studied 120 SNPs that had previously been related to COVID-19, the coagulation cascade and the metabolism of COVID-19 treatments (Supplementary Table S1) (13). The second study (from now on study B) included 1,350 patients between March 29th 2020 and December 31st 2021 and mainly focused on 29 SNPs related to the regulation of immune, complement and coagulation pathways (Supplementary Table S2) (manuscript in preparation).

To enroll a significant number of patients with viremia determination that would enable assessment of the relationship

between viremia and COVID-19 related SNPs all participants in studies A and B who had been checked for the presence of viremia, at least one time in the first week of hospitalization ($n = 340$) were selected for the current study (Supplementary Figure S1). All patients were older than 18 years and had confirmed SARS-CoV-2 infection (RT-PCR, antigen or serological testing).

Blood samples for genotyping were collected during hospitalization since all patients included in this study required admission. Plasma samples for viremia quantification were collected during the first week of admission, following the hospital protocols and the criteria of the physician in charge.

All data were collected from the clinical charts and included in an anonymized electronic database.

2.2. Selection of the SNPs genotyped

A total of 38 SNPs were genotyped in the whole population of the study (Supplementary Table S3). As the 340 patients tested for viremia were part of study B (manuscript in preparation), the 29 SNPs analyzed in that study were included in the current manuscript. In study A, 120 SNPs were analyzed (13). However only 107 of the 340 patients were included in study A. Since we could not genotype these 120 SNPs in the remaining 233 patients due to the high cost, we performed a pre-analysis of the importance of these 120 SNPs among the 107 patients included in study A, selecting those with $p < 0.15$, as described below in the statistical analysis section. We selected 9 SNPs which were later genotyped in the remaining 233 patients. Therefore, these 9 SNPs from study A were added to the 29 SNPs from study B.

2.3. Genotyping

In study A, a Maxwell RSC automated DNA extractor (Promega) was used to extract DNA from peripheral blood. A customized genotyping array was designed and the genotype analysis was performed with a QuantStudio 12 K flex thermal cycler along with an OpenArray thermal block (Thermo Fisher Scientific). In study B (ongoing manuscript), DNA was extracted using MagNA Pure 2.0 and MagNA Pure LC DNA Isolation Kit (Roche Life Science, Basel Switzerland). To genotype the selected SNPs, qPCR was performed using QuantStudio 12 k, TaqManTM Genotyping Master Mix and TaqManTM customized 384 plates (ThermoFisher Scientific, Waltham, MA) in Parque Científico of Universidad Autónoma de Madrid. Allelic discrimination was based on allele-specific fluorescence, which was automatically defined by TaqMan SNP Genotyping App (Applied Biosystems Software). To verify assay's accuracy, negative controls and duplicate samples were used.

The candidate SNPs selected from the study A were genotyped by qPCR using a predesigned single nucleotide polymorphism (SNP) Genotyping Taqman Assays (Applied Biosystems, Waltham, MA. Part number in Supplementary Table S3). The assay was carried out following the manufacturer's recommendations; duplicate samples and negative controls were also included to check the accuracy of the genotyping. Each sample's genotype was determined automatically by measuring allele-specific fluorescence on a CFX Touch Real-Time PCR System using the software CFX 3.1 Manager (BioRad, Hercules, CA, United States).

2.4. SARS-CoV-2 RNA extraction, detection and quantification

SARS-CoV-2 viremia was detected by quantitative RT-PCR (QuantStudio™ 5 Real-Time PCR System) (Applied Biosystems) using the TaqPath™ COVID-19 CE IVD RT-PCR kit (Thermo Fisher Scientific). Amplification curves were analyzed with QuantStudio™ Design and Analysis software version 2.4.3 (Applied Biosystems). All plasma samples were included in duplicates in the assay. Viral load quantification was obtained by plotting Ct values through the standard curve and only viremias with mean Ct ≤ 37 (approximately 1.3 log 10, namely 20 copies/mL) and standard deviation (SD) <0.5 in the duplicate test for each gene were considered quantifiable.

2.5. Variables

The main outcome of this study was the detection of SARS-CoV-2 viremia in the first week of hospitalization. A positive viremia was defined as the presence of at least one determination with a viral load above the quantification threshold (20 copies/mL).

Age was considered as an ordinal qualitative variable and was categorized in three groups: <45 years, 45–70 years and > 70 years.

Severe COVID-19 was defined as the need for mechanical ventilation (invasive or non-invasive), high-flow oxygen, or death.

2.6. Statistical analysis

Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for the variables with non-normal distribution. For qualitative variables, frequency and proportions were used. To analyze statistical differences between variables, Student's t test, Mann–Whitney or Kruskall-Wallis tests were performed for quantitative variables, and $\chi 2$ test for qualitative variables.

The selection of the candidate SNPs from study A to genotype in the remaining 233 patients was performed by analyzing the most relevant SNPs in the 107 patients who had all the SNPs genotyped. To this end, the clinical variables associated with viremia in the bivariate analysis in these 107 patients were included in a multivariate logistic regression analysis. Then, each SNP was forced in the model. SNPs with a $p < 0.15$ in the model were selected. Also, an analysis of the variance of the model of each SNP was performed to help make the selection.

Finally, to determine which clinical variables were associated with the presence of viremia, a multivariate logistic regression analysis was performed (Supplementary Table S4). It was first modeled by adding all the variables with a p value lower than 0.15 in the bivariate analysis. The final clinical model was reached through backward stepwise removal of variables with p value higher than 0.15. Then, all SNPs

were independently included in the clinical model. Those SNPs reaching a p value lower than 0.15 were included together in the final clinical model in order to analyze interactions between them. As previously described, we used a stepwise backwards approach to design the best model for predicting viremia. Then, the jackknife method was applied to reduce bias.

All the analyses were performed with Stata 14.0 for Windows (Stata Corp LP, College Station, TX, United States). Figures were depicted with R Studio (R Core Team 2022. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

2.7. Ethics

This study followed the ethical principles of the Declaration of Helsinki and it was approved by the Research Ethics Committee of University Hospital La Princesa, Madrid, (register numbers 4,111 and 4,070). All patients, except those who died, gave oral or written consent to participate, which was registered in their electronic clinical chart. Due to the COVID-19 pandemic emergency, oral consent was accepted as proposed by the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios, The Spanish Agency for Medicines and Medical Devices).

3. Results

3.1. Clinical variables associated with SARS-CoV-2 viremia

The study population included 60.9% male and 79.4% white non-Hispanic patients, with a mean age of 64.5 years (SD 16.6). The most frequent comorbidities were hypertension (40.3%), dyslipidemia (38.5%), obesity (15.9%) and diabetes mellitus (15.4%) as shown in Table 1. Treatment during hospitalization and analytical variables are shown in Supplementary Table S5.

Of all patients, 126 (37.1%) had at least one positive SARS-CoV-2 viremia during the first week of hospitalization. Patients with viremia were more frequently male (72.2% vs. 54.2%, $p = 0.001$), dyslipidemic (45.2% vs. 34.6%, $p = 0.05$), had more severe disease (16.4% vs. 62.7%, $p < 0.0001$) and were more frequently treated with Angiotensin

TABLE 1 Demographic and clinical data by viremia status.

	Study population (*n* = 340)	No viremia (*n* = 214)	Viremia (*n* = 126)	*p* value
Age; mean (SD)	64.5 (16.6)	63.5 (18.3)	66 (13.2)	0.19
Male sex; *n* (%)	207 (60.9)	116 (54.2)	91 (72.2)	0.001
Race/ethnicity; *n* (%)				
White, non-Hispanic	270 (79.4)	164 (76.6)	106 (84.1)	0.07
White, Hispanic	63 (18.5)	47 (22)	16 (12.7)	
Afrodescendent	1 (0.3)	1 (0.5)	0	
Asian	6 (1.8)	2 (0.9)	4 (3.2)	
Hypertension; *n* (%)	137 (40.3)	81 (37.9)	56 (44.4)	0.23
Dyslipidemia; *n* (%)	131 (38.5)	74 (34.6)	57 (45.2)	0.05
Diabetes mellitus				
Without organ damage	41 (12.2)	22 (10.3)	19 (15.1)	0.43
With organ damage	11 (3.2)	7 (3.3)	4 (3.2)	
Obesity; *n* (%)	54 (15.9)	34 (15.9)	20 (15.9)	1
Dementia; *n* (%)	14 (4.1)	12 (5.6)	2 (1.6)	0.07
Chronic Obstructive Pulmonary Disease; *n* (%)	32 (9.4)	24 [24 (11.2)]	8 (6.4)	0.14
Cancer; *n* (%)				
Without metastasis	5 (1.5)	4 (1.9)	1 (0.8)	0.54
With metastasis	1 (0.3)	1 (0.5)	0	
Severe COVID-19	114 (33.5)	35 (16.4)	79 (62.7)	<0.0001
Previous treatment				
Angiotensin Converting Enzyme Inhibitors; *n* (%)	48 (14.1)	20 (9.35)	28 (22.2)	0.001
Angiotensin Receptor Blocker; *n* (%)	66 (19.4)	47 (22)	19 (15.1)	0.12
Anticoagulants; *n* (%)	31 (9.1)	18 (8.4)	13 (10.4)	0.54
Antiplatelets; *n* (%)	48 (14.1)	26 (12.2)	22 (17.5)	0.17
Systemic glucocorticoids; *n* (%)	9 (2.7)	5 (2.3)	4 (3.2)	0.64
Immunosuppressants; *n* (%)	11 (3.2)	8 (3.7)	3 (2.4)	0.49

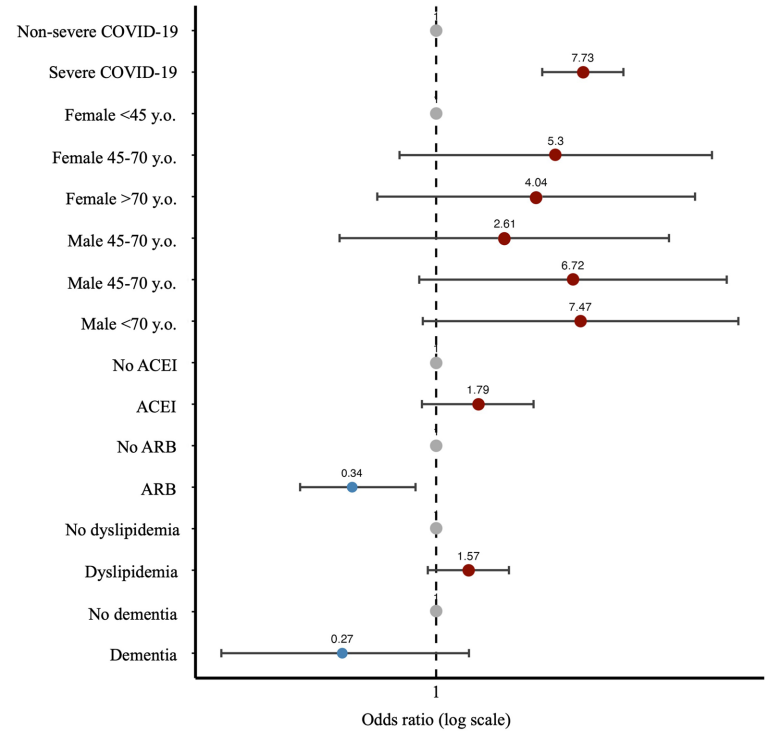

FIGURE 1
Clinical model. Forest plot with the Odds ratio and 95% Confidence Interval of each variable in the clinical model. Blue dots: protective effect against viremia. Red dots, favors viremia. ARB, Angiotensin II Receptor Blocker; ACEI, Angiotensin Converting Enzyme Inhibitor; y.o.: years old.

Converting Enzyme Inhibitors (ACEI) (22.2% vs. 9.4%, $p = 0.001$), as described in Table 1.

Multivariate analysis shown in Supplementary Table S6 and Figure 1 demonstrated that viremia was higher in males above 45 y-o compared to women younger than 45 y-o (OR 6.72 for 45 to 70y-o and OR 7.47 for >70 y-o; $p = 0.08$ and $p = 0.07$ respectively), in those with dyslipidemia [OR 1.57 (95%CI 0.89–2.76); $p = 0.12$], severe COVID-19 [OR 7.73 (95%CI 4.39–13.62); $p < 0.0001$], and those treated with ACEI (OR 1.79 [95%CI 0.82–3.89]; $p = 0.14$). By contrast, patients with dementia [OR 0.27 (95%CI 0.05–1.58); $p = 0.147$] and treatment with Angiotensin Receptor Blocker (ARB) [OR 0.34 (95%CI 0.34–0.7); $p = 0.007$] had viremia less frequently.

3.2. Genetic factors associated with viremia

Once the clinical model was established each of the 38 SNPs (9 from study A and 29 from study B) were individually included/forced in the model (Supplementary Table S7). Among them, 15 reached a value of $p<0.15$: rs33980500, rs13196377 and rs13190932 (*TRAF3IP2*), rs11052877 (*CD69*), rs2071746 (*HMOX1*), rs713400 (*TMPRSS2*), rs78958998 (*SERPING1*), rs541862 (*CFB*), rs438781 (*CFHR1*), rs12408446 (*CFHR3*), rs731034 (*COLEC11*), rs2660 (*OAS1*), rs280500 (*TYK2*), rs896 (*VIPR1*) and rs885863 (*VIPR2*). Of the three SNPs in *TRAF3IP2*, only rs33980500 was considered, as the three of them act in the same pathway and this SNP had the best performance. Also, rs43878 in *CFHR1* and rs12408446 in *CFHR3* were excluded because they had a high number of missing values. The rest of SNPs were included altogether with the clinical variables in order to determine interactions between them and also with clinical variables.

Interestingly, in this last composite multivariate analysis (Table 2) most variables, especially the relationship with age and sex, improved their association with viremia both in terms of OR and value of p, except for rs713400 in *TMPRSS2* which slightly worsened. Thus, after adjustment by clinical and therapeutic variables the presence of the minor alleles of rs2071746 (*HMOX1*; T/T genotype OR 9.9 $p < 0.0001$), rs78958998 (probably associated with *SERPING1* expression; A/T genotype OR 2.3, $p = 0.04$ and T/T genotype OR 12.9, $p < 0.0001$), and rs713400 (eQTL for *TMPRSS2*; C/T + T/T genotype OR 1.86, $p = 0.10$) were associated with higher risk of viremia, whereas the minor alleles of rs11052877 (*CD69*; A/G genotype OR 0.5, $p = 0.04$ and G/G genotype OR 0.3, $p = 0.01$), rs2660 (*OAS1*; A/G genotype OR 0.6, $p = 0.08$), rs896 (*VIPR1*; T/T genotype OR 0.4, $p = 0.02$) and rs33980500 (*TRAF3IP2*; C/T + T/T genotype OR 0.3, $p = 0.01$) were associated with lower risk of viremia. The predicted probability of viremia per genotype of every significant SNP in this model is shown in Figure 2.

4. Discussion

After 3 years of pandemic, COVID-19 remains as a very heterogeneous clinical picture with few reliable biomarkers for severity prediction at the beginning of disease. Among them, the presence of SARS-CoV-2 viremia seems to be the most solid (5). Although several genome wide analysis studies have been performed to find genetic variants associated with disease severity,

TABLE 2 Final model of variables predicting viremia.

	OR (95%CI)	*p* value
Age and sex (reference female <45 years)		
Female 45–70 years	21.99 (5.17–93.55)	<0.0001
Female >70 years	8.69 (1.94–38.99)	0.005
Male <45 years	6.06 (1.22–30.17)	0.03
Male 45–70 years	21.00 (5.62–78.54)	<0.0001
Male >70 years	11.02 (2.69–45.22)	0.001
Severe COVID-19	11.13 (5.27–23.50)	<0.0001
Angiotensin Converting Enzyme Inhibitors	2.40 (0.99–5.82)	0.052
Angiotensin II Receptor blocker	0.41 (0.16–1.10)	0.08
CD69 rs11052877 (reference A/A)		
A/G	0.48 (0.24–0.96)	0.04
G/G	0.29 (0.11–0.74)	0.01
HMOX1 rs2071746 (reference A/A)		
A/T	1.85 (0.86–3.99)	0.11
T/T	9.86 (3.42–28.42)	<0.0001
SERPING1 rs78958998 (reference C/C)		
C/T	2.32 (1.02–5.28)	0.04
T/T	12.90 (3.91–42.63)	<0.0001
TMPRSS2 rs713400 (reference C/C)		
C/T + T/T	1.86 (0.88–3.94)	0.10
TRAF3IP2 rs33980500 (reference C/C)		
C/T + T/T	0.34 (0.15–0.78)	0.01
OAS1 rs2660 (reference A/A)		
A/G	0.56 (0.29–1.07)	0.08
G/G	0.50 (0.13–1.99)	0.33
VIPR1 rs896 (reference C/C)		
C/T	0.80 (0.40–1.60)	0.52
T/T	0.35 (0.15–0.83)	0.02

CI, Confidence Interval; OR, Odds Ratio.

to the best of our knowledge, this is the first study that has assessed the relationship between different genetic variants and SARS-CoV-2 viremia. Our results show than only one genetic variant related with SARS-CoV-2 replication (rs713400 for *TMPRSS2*), and four related with inflammation/immune regulation (rs33980500 for *TRAF3IP2*, rs11052877 for *CD69*, rs2071746 for *HMOX1* and rs78958998 for *SERPING1*) were associated with the presence of viremia.

These results were obtained under careful adjustment by several confounding variables previously suggested as factors associated with COVID-19 severity (3, 21). On the other hand, we must take into account that severity and viremia correlate. However, after adjusting our analysis by COVID-19 severity, the 7 SNPs described remained significant (except for rs713400 in *TMPRSS2* and rs2660 in *OAS1*), meaning that their association with viremia was independent of severity (Supplementary Table S8). This approach allowed us to realize that both genetic and clinical variables improved their performance when they were analyzed together, suggesting that the mechanisms leading to viremia and, therefore, COVID-19 severity involve complex interactions between genetic, sociodemographic, therapeutic and clinical factors. Furthermore, the most important variables to predict viremia seemed to be age and sex, supporting that, as in many other diseases, genetic background is made up of many items with a low contribution by each one (22, 23).

TMPRSS2 encodes a transmembrane protease serine 2 involved in SARS-CoV-2 entry into host cells, by cleaving the spike (S) protein (24). rs713400 location in the 5'UTR of *TMPRSS2* could influence the expression of this gene (25). Our data indicate that carrying one copy of the T allele in rs713400 could be associated with higher prevalence of viremia, although after adjusting by COVID-19 severity this SNP was not significant (data not shown: $p = 0.004$ in a previous model without severity). Taking into account the role of *TMPRSS2* in viral entrance, this SNP could be associated with both viremia and severity. Thus, changes in *TMPRSS2* expression could modify the ability of SARS-CoV-2 to infect host cells and disseminate. In addition, several authors have assessed the influence of genetic variants of *TMPRSS2*, finding that some SNPs such as rs12329760 or rs75603675 are associated with COVID-19 severity (13, 15, 26–28).

Regarding immune system modulation, *TRAF3IP2* encodes for ACT1, a signaling adaptor involved in the regulation of IL-17-dependent immune responses and the activation of NF-κB (29). The variant rs33980500 is mainly associated with psoriasis and is located in a coding region of this gene, causing a change from aspartic to asparagine. Functional assays have found that this change causes a reduced binding of TRAF6 to ACT1, thereby leading to a decrease in IL-17 and Th17 responses (30, 31). In this regard, it has been proposed that Th17 cells play an important role in COVID-19 by promoting a proinflammatory immune response, with a correlation between intense Th17 responses and COVID-19 severity (32). Patients carrying the T allele in rs33980500 might have a weaker activation of IL-17-dependent proinflammatory pathways with a better viral control.

CD69 also plays an important regulatory role in the immune system. CD69 deficient mice display more severe clinical pictures in the collagen induced arthritis and autoimmune myocarditis murine models (33, 34) and show an enhanced differentiation toward Th17 cells (35). In addition, in humans *CD69* expression is decreased in Treg cells from patients with systemic scleroderma (36) and response to tocilizumab is higher in rheumatoid arthritis patients homozygous for the mayor allele of rs11052877 (37). Here, we have described that patients carrying the minor allele of rs11052877 show a lower risk of SARS-CoV-2 viremia, in an additive fashion. In addition, we previously reported that patients with viremia show higher levels of IL-6 compared to those without viremia (38), and therefore, higher possibility of having a good response to tocilizumab (39). Although there are no studies on the role of rs11052877 in *CD69* expression, this SNP is located in the 3' UTR which usually involves regulatory functions. Accordingly, it is tempting to propose that patients carrying the minor allele of rs11052877 could have higher levels of *CD69* expression, therefore leading to decreased Th17 responses to the virus allowing less inflammatory responses though with a better control of viral spreading.

VIPR1 encodes the Vasoactive Intestinal Peptide (VIP) receptor type 1, called VPAC1. Through its binding to VPAC1 (constitutively expressed) o VPAC2 (inducible), VIP is involved in the anti-inflammatory response by promoting the expression of

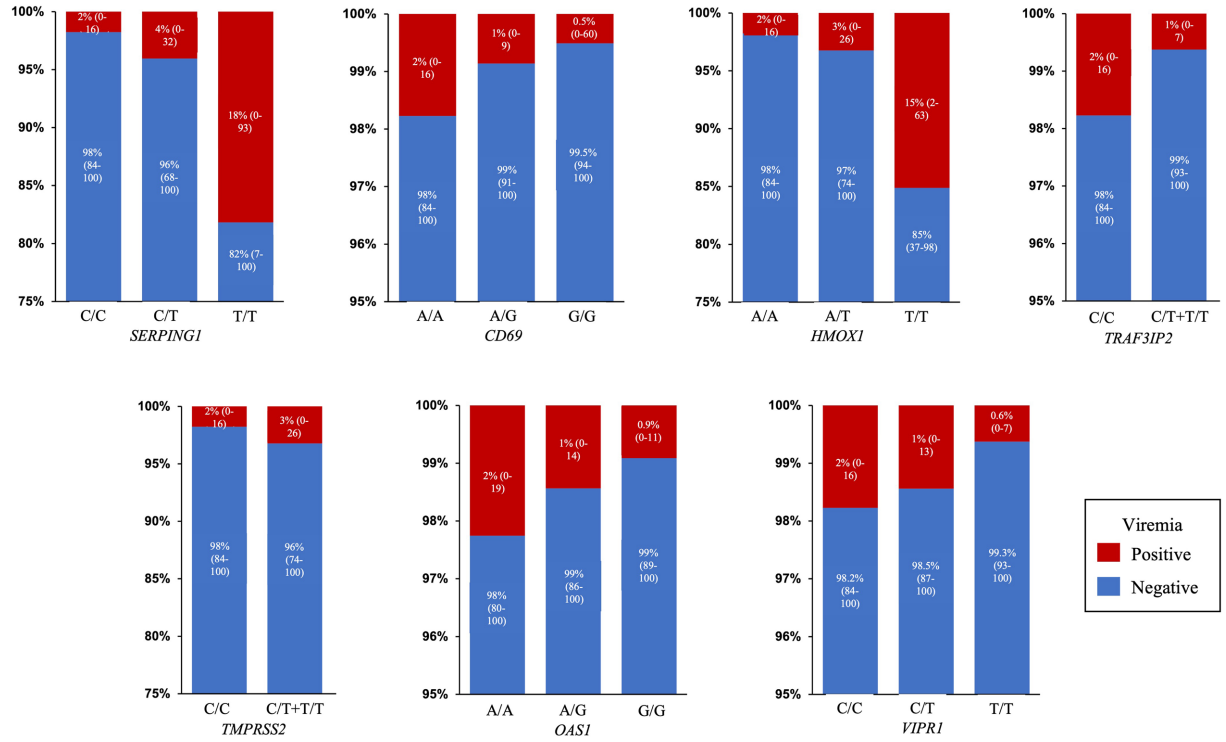

FIGURE 2
Predicted probability of viremia. Percentage and 95% Confidence Interval of predicted probability of viremia for each SNP genotype in the final model: *SERPING1* (rs78958998), *CD69* (rs11052877), *HMOX1* (rs2071746), *TRAF3IP2* (rs33980500), *TMPRSS2* (rs713400), *OAS1* (rs2660) and *VIPR1* (rs896).

anti-inflammatory cytokines and inhibiting the production of pro-inflammatory cytokines such as TNF-∝ or IL-12 (40). In addition, VIP also plays a role in the regulation of Th cells, decreasing the profile of cytokines related to Th1 and Th17, inhibiting Th17 and its pathogenic phenotype (40). The rs896 in the 3'UTR of *VIPR1* has been shown to regulate the expression of VPAC1. The presence of the C allele has been associated with a decreased gene expression and an enhanced binding of the miRNA 525-5p, which decreases VPAC1 expression (41). This SNP has not been studied in COVID-19, but VIP levels were increased in patients with severe disease and correlated with lower levels of inflammatory biomarkers and survival of those patients (42). In this regard, we show that the T allele of rs896 was associated with lower risk of viremia, probably due to an increased expression of VPAC1 compared to C allele, promoting an anti-inflammatory response and the inhibition of Th17.

OAS1 (2′-5′ oligoadenylate synthetase 1) is part of the interferon I pathway and its main role is the activation of L RNAse, which is involved in the control of viral dissemination by degrading viral RNA (43). rs2660 in the 3' UTR of *OAS1* has been previously associated with SARS-CoV infection, being the genotypes A/G and G/G protective (44). This SNP has also been studied in COVID-19, the study of Banday et al. found that the A allele entailed higher risk of hospitalization, as well as lower viral clearance efficiency (although this was not significant) (45). Probably these results are due to an increased enzymatic activity in OAS1 associated to the G/G genotype, the Neanderthal variant, compared to A/A genotype (46, 47). In our cohort, the A/G genotype had a tendency ($p = 0.08$) to be protective against viremia, which is consistent with the evidence described, as the G allele is associated with increased OAS1 activity and thus, viral clearance.

Another gene related to COVID-19 pathogenesis is *HMOX1*, which encodes heme oxygenase one (HO-1), a protein involved in heme catabolism with anti-inflammatory effects (48). HO-1 levels are associated with acute respiratory distress syndrome (ARDS) (49, 50), as well as with COVID-19 severity (51, 52) and this gene has been proposed as a therapeutic target for this disease (53–55). The SNP rs2071746 has not been linked specifically to COVID-19 but Ono et al. showed that the A allele increased *HMOX1* promoter activity compared to the T allele (56, 57). This fact could lead to a protective anti-inflammatory and antiviral effect of the A allele by increasing the expression of IL-10 and the interferon signaling pathway as well as promoting the switch to anti-inflammatory M2 macrophages (58–60). This fits well with our observation that patients homozygous for the T allele of rs2071746 show higher levels of viremia.

Finally, and also in accordance with the notion that excessive inflammatory responses can be associated with lower capability to control SARS-CoV-2 spreading, rs78958998 has been described as an eQTL for *SERPING1*, and one study suggested its association with COVID-19 (61). *SERPING1* encodes the protein C1 inhibitor (C1INH) which is involved in complement and coagulation pathways as well as contact system by inhibiting C1r and C1s or activated factor XI and XII, among others (62). Although C1INH levels are increased in patients with COVID-19, it might be insufficient to control thromboinflammation. Reasons for this include a relative deficiency due to an uncontrolled activation of complement and coagulation cascades, together with the limitation of its regulatory activity caused by the interaction with SARS-CoV-2 proteins (63, 64). Since complement activation is involved in virus neutralization and

virolysis, impaired *SERPING1* expression could contribute to virus dissemination and viremia (65).

Although the implication of the variants presented in this manuscript in the prevalence of viremia is attractive and based on the function of each of the genes, many of the SNPs described above have not been studied in COVID-19 patients. In addition, functional studies are needed to correlate these variants with their gene expression and protein activity.

The main limitation of this study is the small sample size, which was affected by the previous studies of our group. However, this sample size was enough to find significant differences in those SNPs with the strongest effect. Obviously, a wider approach in terms of genetic variations would be desirable; however, the study of a higher number of genes was precluded by two issues, the high economic cost of these studies, and the need of a larger number of patients. Another important limitation is the lack of data about SARS-CoV-2 variants and vaccination status, which could differentially affect infectivity and prevalence of viremia. However, most of the patients suffered from COVID-19 between the first and the fourth waves of the pandemic, so the effect of vaccination could be considered minor.

In conclusion, SARS-CoV-2 viremia was associated with variants of rs2071746 (*HMOX1*) rs78958998 (*SERPING1*), rs713400 (*TMPRSS2*), rs11052877 (*CD69*), rs33980500 (*TRAF3IP2*), rs2660 (*OAS1*) and rs896 (*VIPR1*), after adjusting by age and sex, COVID-19 severity and treatment with ACE inhibitors and Angiotensin II blockers. Nevertheless, these results should be validated in a different cohort.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number (s) can be found at: https://doi.org/10.5281/zenodo.7882217.

Ethics statement

The studies involving humans were approved by Research Ethics Committee of University Hospital La Princesa, Madrid. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because due to the COVID-19 pandemic emergency, oral consent was accepted as proposed by the AEMPS (Agencia Española de Medicamentos y Productos Sanitarios, The Spanish Agency for Medicines and Medical Devices).

Author contributions

ER-V, LC, and IG-Á designed the study and wrote the first draft of the manuscript. ER-V, AL, JG-R, GVG, PZ, MC, LR, MS, CR, AV, JR, CM, JH, FA, IS, DR, RG-V, CSF, and RPG included patients in the study and collected data. RC-R, SC-O, PD-W, AM-J, CM-C, and EF-R extracted and processed samples. ER-V, SC-O, PD-W, AT-M, and NZ-C performed laboratory determinations. ER-V, NM, and IG-Á analyzed data. ER-V, PZ, SC-O, PD-W, AT-M, NM, RC-R, NZ-C, AM-J, AL, JG-R, GVG, AV, JR, CM, JH, PD-F, FA, IS, DR, RG-V, CSF, EF-R, IG-Á, and LC reviewed the final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

FA, has been consultant or investigator in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Aptatargets, Chemo, FAES, Farmalíder, Ferrer, Galenicum, GlaxoSmithKline, Gilead, Italfarmaco, Janssen-Cilag, Kern, Normon, Novartis, Servier, Teva and Zambon. IG-Á reports grants from Instituto de Salud Carlos III, during the course of the study; personal fees from Lilly and Sanofi; personal fees and non-financial support from BMS; personal fees and non-financial support from Abbvie; research support, personal fees and non-financial support from Roche Laboratories; research support from Gebro Pharma; non-financial support from MSD, Pfizer and Novartis, not related to the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1215246/full#supplementary-material

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Impact of the 7/14/2016 Nice terrorist attack on pediatric emergency department visits thanks to syndromic surveillance: a descriptive study

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Objective: Study the impact of 14th July 2016 Nice terrorist attack on Pediatric Emergency Department (PED) visits by youth under 18 years of age.

Methods: PED visits diagnoses (ICD10) were clustered and analyzed based on retrospective data from the syndromic surveillance system of the Children's university hospital of Nice (Southern France). The studied period ranges from 2013 to 2019, i.e., 3 years before and after the terrorist attack of 14th July 2016.

Results: Among 416,191 PED visits, the number of visits for stress in 4–17 years old appeared to increase in the 3 years after the attack compared to the 3 years before, particularly in September 2016 (acute effect) with 11 visits compared to an average of 2.3 visits per month from September 2013 to 2016 ($p = 0.001827$). In September 2017, we noticed 21 visits compared to an average of 4.8 visits per month during the following period (2013–2019). In 2017, PED visits for stress among 4–17 year olds were higher in comparison to the other years of the study: 107 visits compared to an annual average of 57.

Conclusion: To our knowledge, this is the first study of the use of the pediatric care system before and after a terrorist attack involving syndromic surveillance. This suggests acute and long-term effects of the terrorist attack on PED use by youth for mental health issues. Further studies of the pediatric care system involving syndromic surveillance are needed in the context of mass violent events, such as terrorist attacks.

KEYWORDS

stress, child and adolescent psychiatry, psycho-trauma, syndromic surveillance, terrorist attack

Introduction

The city of Nice (south of France) was hit by an Islamist terrorist attack with a truck on French national day, on 14 July 2016. The death toll rose to 86 killed people, including 15 children with 458 injured and more than 30,000 witnesses of the event. According to international classifications (ICD 11 and DSM 5-TR), a terrorist attack is a grade event resulting in a potential psycho-trauma: a psycho-trauma exposure according to the DSM. Psycho-trauma, can have consequences on physical health, social relationships, and quality of life. They can also generate psychiatric disorders. Post-traumatic Stress Disorder (PTSD: DSM 5-TR, 2023) is the most studied of them. Other disorders can occur and be associated with PTSD, such as anxiety, mood disorders like depression, addiction and Attention Deficit Disorder (ADD), with or without Hyperactivity which can all occur past the initial traumatic event and can vary long after (1–3). Psychological and psychiatric consequences of a sole exposure to a traumatic event, as terrifying and shocking as it could be [type 1 trauma according to Terr (4)], can be extremely severe with children, with a possible toll on their development (5). These consequences can differ from an adult population and can vary according to the child's age and depend on his entourage's reactions, most notably his parents' (6).

In Nice, the psychiatric impact after the terrorist attack of 14th July 2016 was heavy within the pediatric population. An epidemiologic clinical study led by the Nice University service of the child and adolescent psychiatry, showed that 62% of the 271 children admitted suffered from PTSD, regardless of their age (7, 8). This terrorist attack happened not far (around 200 m) from the Children's university hospital of Lenval. It includes pediatric emergencies, located on one single site and which has admitted on average around 60,000 pediatric emergencies per year since 2013 (fourth children's admittance in France). During and after the attack, the Lenval Hospital had to produce an exceptional and swift response to the gravity of the event (several fatal casualties) and the admittance high demands (9–11).

Children are indeed an extremely vulnerable population, this coming from their lower emotional maturity, which does not allow them to comprehend the event they have experienced and does not allow them to make sense of it. Moreover, exposure to traumatic events in childhood is a risk factor that increases the chances of developing PTSD later in life (12). The emotional state of the adult accompanying the child is also an important factor, regulating the possible apparition of disorders in the wake of a psycho-trauma. In the context of a terrorist or mass violence attacks, taking this into consideration is of utter importance as parents are often affected by the same event. On a pathopsychological level, the different zones of the child's brain show an unequal growth (13). The frontal zones, which show a subsequent growth (until the end of the adolescence), can be more sensitive to later psycho-traumas, opposed to the hippocampal regions, which are generally more affected by stress induced events from early childhood (14, 15).

In the wake of the event (from the second day to the first month after the psycho-trauma), the child can develop an acute stress, anxiety, depression, regressive behaviors, and somatizations. After a month, the child can experience nightmares, somatizations, disturbed cognitive schemes with a refusal to learn, fear of separation and depression, delayed growth, or regressive behaviors (16). Before the age of 3, the child usually reacts displaying biophysiological, motor, eating and attachment (development, anorexia, insomnia, fits of rage and cries or stillness) disorders. After the age of 3, we can observe intrusive reminiscences of the psycho-trauma, behaviors featuring avoidance of fear of separation (possibly leading to an anxious school refusal), or aggressiveness and regressiveness. However, these consequences can be altered with an adapted and early care of the child (17, 18).

The link between somatic symptoms and post-traumatic stress has been studied in an adult population (19). Exposure to traumatic events in childhood has serious and damaging effects on the mental and physical health of adults (20). Similar adverse effects probably exist in children, but data are lacking. Using a syndromic surveillance system should allow for better measurements (and better care) for patients affected by these type of events (21). Yet, no studies of this kind is currently available to our knowledge to measure the impact of psycho-trauma on children and its consequences on the use of the pediatric care system. Terrorist attacks have been more frequent these last decades worldwide (even among pacified countries). Hence, understanding their impact could be useful to the French health care system but also to European and worldwide countries.

The aim of this study is to investigate the psycho-traumatic impact of the Nice terrorist attack on children under the age of 18 by exploring changes in complaints from users of the Nice (France) pediatric healthcare system (pediatric emergency departments) after this mass violence event.

Materials and methods

Study scheme

This study is retrospectively based on the data from the pediatric emergencies from the Children's university hospital of Lenval, from 2013 to 2019, meaning 3 years before and after the terrorist attack of 14 July 2016.

Setting

Nice is France's 5th largest city in terms of population. The French National Institute for Statistics and Economic Studies (Insee) estimated that in 2016, Nice had 54.667 children under the age of 15 (15.8% of the total population of 345,998). Nevertheless, the Lenval hospital is the only establishment in the city to deal with pediatric emergencies.

Collecting data

Collecting data came from the e-SurSaUD® database, which compiles emergency room visits ("résumés de passages aux urgencies"—RPU) of the Children's University Hospital of Lenval. Each day, every emergency room visits are automatically sent to "Santé Publique France" (the French National Public Health Agency) as part of the syndromic surveillance system.[1] The main variables coming from the emergency room visits are administrative variables (identification number of the hospital, date, and time of admittance,

1 https://www.santepubliquefrance.fr/surveillance-syndromique-sursaud-R

etc.), demographic variables (gender, date of birth, etc.) and medical variables (main diagnosis, associated diagnosis, etc.). Medical diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD10) and syndromic clusters, which include one or several codes, are built by the French National Public Health Agency for health monitoring and epidemiology surveillance. Collected variables for the study include: the patient's age (at the time of consultation), the date of emergency room admittance and the main and/or associated diagnosis following the patient's admittance (several diagnoses are possible). With this device, we have collected data for the city of Nice.

Analyzing data

The analysis was focused on the emergency room visits of the Lenval university hospital for 26 syndromic clusters, comprised of diagnoses given at the pediatrics emergencies, each including CIM codes between 1 and 2,487 (see Supplementary Appendix 1). Out of those 26 specific syndromic clusters, 10 are dedicated to patients aged between 0- and 3-year-olds (Supplementary Appendix 1). We have also considered the "any causes visits" criteria, which includes all coded visits regardless of the diagnosis.

To study the event's acute effects (the differences seen between a time of 3 months before and after the attack) and the delayed ones (the differences seen between a time of 3 years before and after the attack), we have considered the time evolution of the number of visits and the proportion of activity for each of the syndromic clusters on a weekly and monthly basis. We used *Chi2* and Wilcoxon tests to assess a comparison of the proportion of emergency department visits based on before and after the event. The patients' age varied between 0- and 3-year-olds and 4- and 17-year-olds. The 0–3-year-old group included newborns, infants, and non-verbal children with a different symptomatic expression from older children and represented a major proportion of emergency department visits (53.5% of the total number of 0–17-year-old visits during the same period). On the other hand, the 4–17-year-old group was not analyzed in homogeneous subcategories to avoid any risks of over-accentuating the representation of this age group, which only represented 46.5% of the total number of 0–17-year-old visits.

Results

Global activity

On this period, 416,191 visits were registered at the Lenval Hospital (222,748 visits from the 0- to 3-year-olds and 193,443 visits from the 4- to 17-year-olds), giving an average number of 59,456 visits per year (31,821 for the 0- to 3-year-olds and 27,635 for the 4- to 17-year-olds, see Supplementary Appendix 2).

Acute effects

Analyzing the syndromic clusters of the 0–3 years-old and the 4–17 years-old over the period of 3 months after the 14 July 2016 attack did not highlight any acute effects. Analyzing the acute effects (3 months post-attack) considering a one-month period, we find a significant difference for the month of September 2016 (compared to September 2013, 2014, and 2015) for the variable stress among 4–17 year-olds. For the months of September 2013 to 2015 we find an average of 0.08 passages per day versus 0.37 per day in 2016 ($p = 0.001827$).

Delayed effects

Within the 0–3-year-old group, we could not observe any delayed effects during the 3-year period following the attack as opposed to the 3-year period prior to the event. This very same analysis of the 3-year period following the attack allowed us to measure a spike of emergency department visits for stress in September 2017 within the 4–17-year-olds (Figure 1). This matches the time children were back to school after the one-year anniversary of the attack. Twenty one visits for an average per month over the period of study of 4.8 visits, a number largely outside the 95% confidence interval normally observed for this monthly average (CI: [4.0–5.5]). This meant a proportion of 0.9% visits for the 4–17-year-olds (against an average 0.2% over the 2013–2019 period; see Supplementary Appendix 2). However, no similar spike for emergency department visits for stress within the 4–17-year-olds was registered for the months of September in 2018 (4 visits) and 2019 (6 visits). More generally, in 2017, there were far more emergency department visits for stress within the 4–17-year-olds in comparison to the other years of the study: 107 visits for an annual average of 57. The details of the 17 ICD-10 codes constituting the stress syndromic cluster are presented in Supplementary Appendix 3.

Discussion

No differences in the number of visits for the 26 syndromic clusters was shown between the 3-month period prior to and the 3-month period following the attack analyzing the 3 months as a grouped variable. Considering a one-month period, we found a significant difference for the month of September 2016 (compared to September 2013, 2014, and 2015) for the variable stress among 4–17 year-olds ($p = 0.001827$). This period was chosen as it usually matches a time delay, after which the appearance of PTSD after a traumatic event is very unlikely [3.5% according to Santiago et al. (22)]. This means that an immediate effect would be measured after the attack on the sole basis of emergency department visits. The organization of a psychiatric care unit right after the attack, put up by the university's child and adolescent psychiatry service of Nice in combination with the help of regional and national services provided to the affected population, seems to have been an appropriate response (23, 24). Desite this, the acute effect measured in terms of number of visits could have been greater. On one hand, data (number and patterns of the visits) from the public health emergency preparedness and response department ["Établissement de Préparation et de Réponse aux Situations Sanitaires Exceptionnelles (EPRUS)] and from medical and psychological emergencies crisis units [cellules d'urgence médico-psychologique (CUMP)] were not counted within pediatrics emergencies. On the other hand, a beneficial effect may have occurred during this time of limited emergency response, which

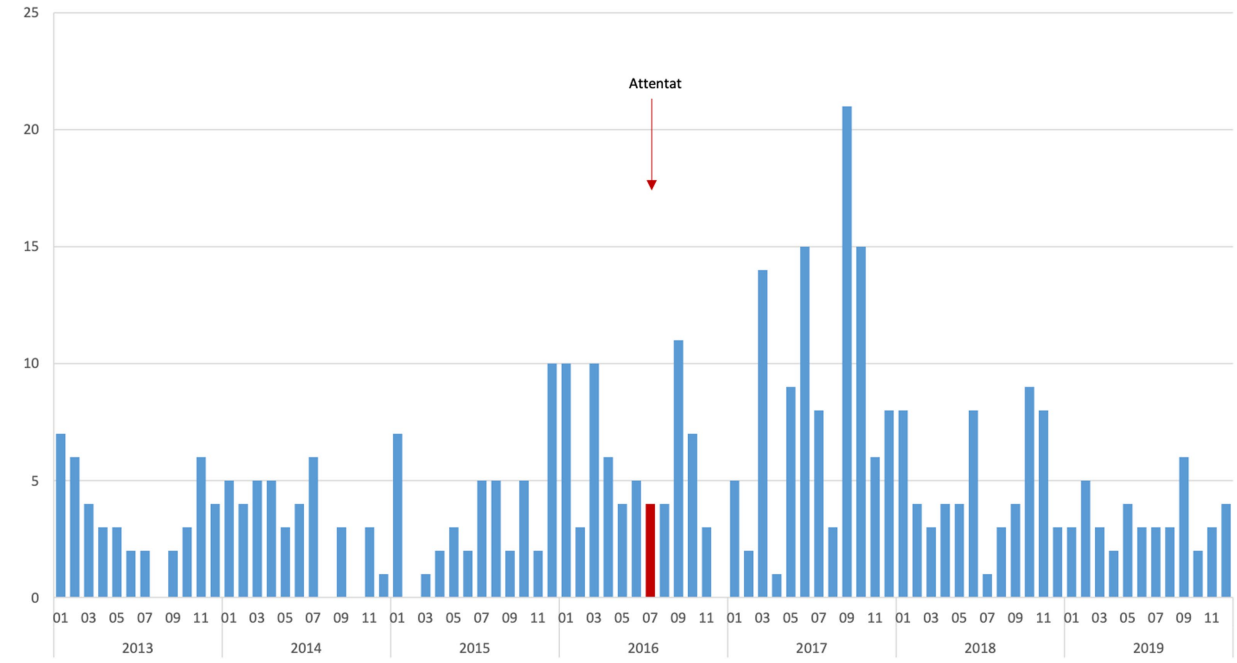

FIGURE 1
Monthly number of emergency department visits for stress in the 4–17-year-old children, Lenval university hospital, 2013–2019.

could have reduced the necessity for systematic emergency department visits for stress right after this post-attack period.

During the 3 years that followed the attack, the number of emergency department visits for stress within the 4–17-year-olds seemed to rise in comparison to the 3 years prior to the attack, most notably in 2017 (one-year anniversary of the attack). We have also observed a spike of visits for stress within 4–17-year-olds in September 2017. This phenomenon means there was a probable rebound of anxiety following the first national commemoration of the event (25), which took place on 14 July 2017. Following this, going back to school for children probably meant an additional source of stress (as we have already assumed for the peak of stress among 4–17 year-olds at the start of the school year in September 2016, 2 months after the attack), combined with the stress experienced during the national commemoration, which had happened only 2 months before. This security obsessed context, caused by the post-attack security plan ("Vigipirate") and its strict policy forbidding parents to accompany their children within the school premises, most probably had its effects in terms of stress. Indeed, Virginia Gil-Rivas et al. (26) have demonstrated that 1 year after the 9/11 attacks in 2001, the traumatic impact after the event was not limited to teenagers that were exposed to it but that it also had repercussions to teenagers that had psychiatric antecedents or experienced learning difficulties, while also taking into consideration their parents' anxiety level. Thus, in our population that goes to school (from kindergarten to high school), going away on holiday to avoid the commemoration (avoidance syndrome) probably had a significative impact and meant an increase of emergency visits when those children came back from their holiday and went back to school after this summer of commemoration of the attack. This is confirmed as for the years that followed, 2018 and 2019, no such increase of visits for stress was registered as it was in 2017. Furthermore, we have double checked with SurSAUD's data (for stress syndromic cluster regarding the 5–14-year-old category) coming from the PED of Marseille (a city that was not directly affected in this period by a terrorist resulting with a similar number of casualties) and from the national level (Whole French territory). We have not registered any increase of visits for stress over the whole year of 2017, nor for the month of September in particular. This specific argument validates the observed effects at the pediatric emergency department of Nice during the anniversary of the terrorist attack.

Thereby, analyzing data from the pediatrics emergencies allowed us, retrospectively, to issue a warning on the probable health risk, depending on age (stress within the 4–17-year-olds) and to expose the magnitude of its effect and its persistence in time (more than 1 year after the event).

Limitations

Although this increase of pediatric emergencies visits for stress may suggest a mental health impact of the 14/07/2016 terrorist attack on the pediatric population of Nice, we cannot ascertain there is direct link of causality.

Indeed, at the time, a device for a live syndromic surveillance that would report all reasons for emergencies visits directly or indirectly linked to the terrorist attack was not set up right after the event nor for a longer period afterwards. We are also not able to analyze in a qualitative manner all the factors triggering or favoring these emergencies visits for stress. PTSD is the psychiatric disorder associated with the highest frequency of somatic complaints (27). Among young people, the most studied potentially traumatic mass events have been disasters triggered by natural hazards (Hurricane Katrina and the Japanese earthquakes). Somatic complaints described and associated with post-traumatic stress include sleep disorders,

fatigue, headaches and abdominal pain (28–30). The link between stress and somatic complaints in the general pediatric population after a terrorist attack, however, has not yet been studied. Likewise, an under-estimation of these visits for stress may have intervened if, in a post-attack period and during the anniversary period, a somatic complaint was not directly attributed to its underlying stress (under-diagnosis and diagnosis with a delayed effect during an ulterior visit).

It is important to note in that sense that during this study period, there was no caring team specialized in child and adolescent psychiatry at the pediatric emergencies of the Lenval university hospital for children. Instead, there was a dedicated team of pediatrists with a child and adolescent psychiatry resident on duty and a senior practitioner on call from home (31). This context could also have led to under-diagnosis of stress syndromic cluster.

To conclude, to our knowledge, this is the first study of the use of the pediatric care system before and after a terrorist attack involving syndromic surveillance in a context of catastrophe with a mass trauma. Our results suggest acute and long-term effects of the terrorist attack on PED use by youth for mental health issues. A live syndromic surveillance device (21, 32) and an analysis of data from the field (private practice medicine, emergency medical service), associated with data from other sites in the country that were not affected, would allow us to understand better the links between the different variations of solicitations for emergency care at the hospital from the population and the effect of the studied catastrophe on the health of that population. A dedicated consultation center was set up by the child and adolescent psychiatry department of the university hospital after this event to measure the effects caused by this psycho-trauma and its long-term negative consequences (33). Further studies will be conducted to measure the benefit it may procure, both on an individual and more global level, for young people admitted for care.

Data availability statement

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

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AF, FA, and SV contributed to conception and design of the study. LM and FF organized the database and performed the statistical analysis. AF wrote the first draft of the manuscript. AF, LM, FF, CV, MG, FA, and SV wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1248993/full#supplementary-material

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Clinical outcome prediction of acute neurological patients admitted to the emergency department: Sequential Organ Failure Assessment score and modified SOFA score

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Background: The aim of this study was to determine the ability of the Sequential Organ Failure Assessment score (SOFA) and modified SOFA score (mSOFA) as predictive tools for 2-day and 28-day mortality and ICU admission in patients with acute neurological pathology treated in hospital emergency departments (EDs).

Methods: An observational, prospective cohort study in adults with acute neurological disease transferred by ambulance to an ED was conducted from 1 January 2019 to 31 August 2022 in five hospitals in Castilla-León (Spain). Score discrimination was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the score.

Results: A total of 640 adult patients with neurological disease were included. For the prediction of 2-day mortality (all-cause), mSOFA presented a higher AUC than SOFA (mSOFA = 0.925 vs. SOFA = 0.902). This was not the case for 28-day mortality, for which SOFA was higher than mSOFA (mSOFA = 0.852 vs. SOFA = 0.875). Finally, ICU admission showed that SOFA was higher than mSOFA (mSOFA = 0.834 vs. SOFA = 0.845).

Conclusion: Both mSOFA and SOFA presented similar predictive ability, with mSOFA being the best predictor for short-term mortality and SOFA being the best predictor for medium-term mortality, as well as for ICU admission. These results in a cohort of patients with acute neurological pathology pave the way for the use of both predictive tools in the ED. The inclusion of these tools could improve the clinical assessment and further treatment of neurological patients, who commonly present the worst outcomes.

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KEYWORDS

acute neurological disease, emergency department, mSOFA, SOFA, mortality

1. Introduction

Recent research has confirmed that the rates of patients attended at emergency departments (EDs) for acute neurological pathologies are approximately 20% of the total cases attended (1–3). Early intervention in the ED is crucial in the clinical evolution of patients with these conditions (4, 5). Its time-dependent component has been extensively studied, and protocols and hospital organization plans have been implemented to improve the interdisciplinary care of these cases (1, 6–8). Based on this, the use of risk scoring systems becomes necessary as a tool to harmonize the evaluation and standardize risk categories. These tools support the risk of early clinical deterioration assessment in patients with diverse conditions and in complex clinical settings. Due to their easy-to-use conception, they can be used in the prehospital setting, in the ED or in other hospital departments (9).

The research carried out with scores in recent years is extremely numerous, resulting in very heterogeneous scoring systems (10). For instance, the combined use with fast-processing biomarkers, especially lactate, improves their predictive ability (11, 12). The Sequential Organ Failure Assessment score (SOFA) is a wide-ranging scale with high implementation in intensive care units (ICUs) and EDs, which provides very adjusted information in various clinical situations (11). Because the original score included numerous laboratory determinations that hindered its use in many dynamic contexts, several modifications have been developed, for instance, quick-SOFA (qSOFA) or modified SOFA (mSOFA), enhancing its scope of application and streamlining the results (1, 5, 13). Particularly remarkable is the mSOFA score, which replaces the measurement of platelets and bilirubin with lactate (a biomarker that improves the predictive capacity of short- and medium-term mortality and adverse events) (14).

The literature in this field has demonstrated the adequate role of risk scoring systems as predictors of adverse events in various acute neurological pathologies (15–17). However, the role of SOFA and mSOFA in these patients has not been studied deeply. Thus, the primary objective was to validate this risk score as a predictive tool for 2- and 28-day mortality, and the second objective was to evaluate the risk score for ICU admission in patients with acute neurological pathology treated in the ED.

2. Methods

2.1. Study design and settings

An observational, prospective cohort study in adults with acute neurological disease transferred by ambulance to an ED was conducted from 1 January 2019 to 31 August 2022. Data collection took place in five hospitals in the Castilla-León region operated by the Public Health System of Castilla-León (SACYL): Segovia Hospital Complex (level II), Burgos University Hospital, Salamanca University Assistance Complex, Rio Hortega University Hospital, and Valladolid University Clinic (level III), complexity levels were assigned following national health system classification based in Hensher et al. (18). Ethical approval was obtained from the Research Ethics Committee of all participating centers (Ref. CEIC 2049, MBCA/dgc, PI 18–895,

TABLE 1 Sequential Organ Failure Assessment score (SOFA) and modified Sequential Organ Failure Assessment score (mSOFA).

		Points				
		0	1	2	3	4
Common items (SOFA and mSOFA)	Respiratory	PaO2/FiO2 > 400 SpO2/FiO2 > 302	PaO2/FiO2 < 400 SpO2/FiO2 < 302	PaO2/FiO2 < 300 SpO2/FiO2 < 221	PaO2/FiO2 < 200 SpO2/FiO2 < 142	PaO2/FiO2 < 100 SpO2/FiO2 < 67
	Renal, Creatinine (mg/dl)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
	Neurologic, GCS (points)	15	13–14	10–12	6–9	<6
	Cardiovascular, MAP (mmHg)	≥70	<70	Dopamine≤5or Dobutamine (any dose)	Dopamine>5, Epinephrine≤0.1, or Norepinephrine≤0.1	Dopamine>15, Epinephrine>0.1, or Norepinephrine>0.1
SOFA items	Coagulation, Platelets ($\times 10^3/\mu L$)	≥150	<150	<100	<50	<20
	Liver, Bilirubin (mg/dl)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
mSOFA items	Metabolic, Lactate (mmol/L)	<2	2.1–3	3.1–4	4.1–6	>6

PaO2/FiO2 ratio, partial pressure of oxygen in arterial blood/fraction of inspired oxygen; SpO2/FiO2 ratio, pulse oximetry saturation/fraction of inspired oxygen ratio; GCS, Glasgow coma scale; MAP, mean arterial pressure.

Ref. CEIm PI010-18, PI 2018 10–119). Registration of the study has been completed in the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization.[1] Informed consent was obtained from all patients or their legal guardians.

2.2. Participants

The study included adult patients (>18 years) who were collected uninterruptedly 24/7/365 and transferred by ambulance to the ED with an acute neurological disease diagnosis. Minors, pregnant females, individuals with acute psychiatric pathologies, those with terminal illness and specialist reports, cases of cardiorespiratory arrest upon ED arrival, patients without informed consent, or those lacking essential information for SOFA or mSOFA scores were excluded.

2.3. Outcomes

The main outcome was mortality at 2 and 28 days (all-cause and in-hospital). As a secondary outcome, ICU admission.

2.4. Measurement and data collection

The complete collected data included demographic variables (sex and age), initial evaluation (heart rate, respiratory rate, temperature, systolic, diastolic, and mean blood pressure, oxygen saturation, fraction of inspired oxygen and level of consciousness), and analytical variables (lactate, platelets, glucose, creatinine, and bilirubin). Additional information was recorded: hospital triage level (all the hospitals use the Manchester Triage system with levels from 1 to 5. Level 1: immediate response, level 2: very urgent, level 3: Urgent. The other two levels were not represented in our cohort and refer to low risk patients), pathology, hospital interventions (computerized axial tomography, ultrasound scan, surgery and coronary/neurovascular intervention) or hospital outcomes (hospitalization and ICU days).

The vital signs were obtained in a triage box by emergency registered nurses (ERNs): oxygen saturation, blood pressure, and heart rate; respiratory frequency was determined by monitoring ventilatory cycles through auscultation for 30 s (or 1 min in irregular breathing or extreme range cases); and neurological status was systematically monitored using the Glasgow Coma Scale (GCS). The analytical parameters (lactate, platelets, glucose, creatinine, and bilirubin) were obtained during the first 8 h of the patient's stay in the ED in the first blood sample collected.

The mSOFA was calculated according to the score determined by Martín-Rodriguez et al. (14), where platelets and bilirubin were replaced by lactate, and the cutoffs for this metabolic biomarker were ≤ 2 mmol/L = 0 points, 2.1 to 3.0 mmol/L = 1 point, 3.1 to 4.0 mmol/L = 2 points, 4.1 to 6.0 mmol/L = 3 points, and > 6.0 mmol/L = 4 points. Table 1 shows a summary score resulting from the sum of points in each variable for SOFA and mSOFA.

2.5. Statistical methods

The collected data were stored in a database created using the software IBM SPSS Statistics for Windows version 20.0. (IBM Corp, Armonk USA). The database was reviewed for the detection of missing data, and no missing data were allowed, i.e., cases with missing data were excluded from the analysis (complete case study.). The final outcomes and predictors were completed by an independent investigator of each hospital through a review of the patients' electronic medical records.

The univariate analysis used for cohort description and to report the association between predictors and the outcome was assessed by the Mann–Whitney U test or the chi-squared test, as appropriate. Categorical variables were described using absolute and relative frequencies. Quantitative variables were described as medians and interquartile ranges (IQR: 25th–75th percentile) because they did not

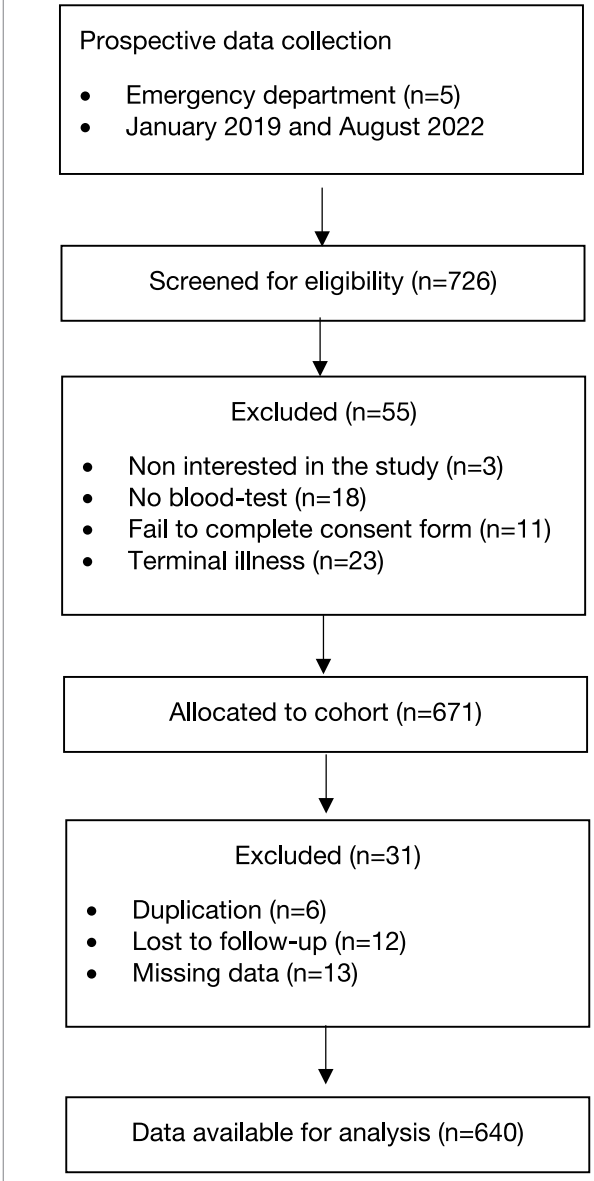

FIGURE 1
Flowchart.

1 https://doi.org/10.1186/ISRCTN48326533

TABLE 2 Comparison of patient variables recorded in the emergency department according to 2-day mortality.

Variables[1]	Total	Survivors	Nonsurvivors 2 days	*p* value and effect size[2]
Number	640 (100%)	581 (91%)	59 (9%)	
Demographic				
Age (years)	67 (52–81)	66 (51–80)	78 (65–83)	$p < 0.001$* (0.15) [T]
Sex				
Male	359 (56%)	325 (56%)	34 (58%)	$p = 0.80$
Female	281 (44%)	256 (44%)	25 (42%)	
Initial evaluation				
Pulse (bpm)	83 (69–95)	82 (70–95)	86 (67–102)	$p = 0.51$
Respiratory rate (bpm)	15 (14–18)	15 (13–18)	15 (15–22)	$p = 0.006$* (0.11) [T]
Temperature (°C)	36.0 (35.8–36.5)	36.0 (35.8–36.5)	36.0 (35.0–36.7)	$p = 0.08$
Systolic Blood Pressure (mmHg)	134 (117–155)	133 (117–152)	146 (105–173)	$p = 0.22$
Diastolic Blood Pressure (mmHg)	76 (65–86)	76 (65–86)	75 (60–97)	$p = 0.91$
Mean Blood Pressure (mmHg)	95 (84–108)	95 (84–107)	100 (73–122)	$p = 0.48$
SpO_2 (%)	97 (95–99)	97 (95–99)	96 (91–100)	$p = 0.11$
SaFi	452 (284–467)	452 (354–467)	182 (96–243)	$p < 0.001$* (0.37) [S]
Glasgow Coma Scale (total)	15 (10–15)	15 (12–15)	3 (3–7)	$p < 0.001$* (0.43) [S]
Eye Opening Response	4 (3–4)	4 (3–4)	1 (1–1)	$p < 0.001$* (0.43) [S]
Verbal Response	5 (3–5)	5 (4–5)	1 (1–1)	$p < 0.001$* (0.43) [S]
Motor Response	6 (5–6)	6 (5–6)	1 (1–3)	$p < 0.001$* (0.45) [S]
Lactate	2.3 (1.5–4.0)	2.1 (1.4–3.6)	4.9 (3.0–7.8)	$p < 0.001$* (0.26) [S]
Platelets	213 (169–260)	215 (170–260)	199 (154–298)	$p = 0.57$
Glucose	132 (109–170)	131 (108–168)	150 (126–203)	$p = 0.002$* (0.13) [T]
Creatinine	0.90 (0.74–1.15)	0.88 (0.74–1.12)	1.09 (0.75–1.76)	$p = 0.002$* (0.12) [T]
Bilirubin	0.51 (0.45–0.66)	0.51 (0.45–0.64)	0.54 (0.46–1.06)	$p = 0.004$* (0.11) [T]
Hospital triage				
Level 1 Immediate response	99 (16%)	69 (12%)	30 (51%)	$p < 0.001$* (0.31) [M]
Level 2: Very urgent	276 (43%)	252 (43%)	24 (41%)	$p = 0.69$
Level 3: Urgent	265 (41%)	260 (45%)	5 (8%)	$p < 0.001$* (0.21) [S]
Pathology				
Seizures	186 (29%)	185 (32%)	1 (2%)	$p < 0.001$* (0.19) [S]
Ischemic stroke	127 (20%)	121 (21%)	6 (10%)	$p = 0.051$
Hemorrhage	118 (18%)	83 (14%)	35 (59%)	$p < 0.001$* (0.34) [M]
Infection	53 (8%)	45 (8%)	8 (14%)	$p = 0.12$
Confusion syndrome	44 (7%)	43 (7%)	1 (2%)	$p = 0.10$
Degenerative disease	23 (4%)	23 (4%)	0 (0%)	$p = 0.12$
Headache	21 (3%)	21 (3%)	0 (0%)	$p = 0.14$
Coma	21 (3%)	15 (3%)	6 (10%)	$p = 0.002$* (0.12) [S]
Vertigo	18 (3%)	18 (3%)	0 (0%)	$p = 0.17$
Tumor	17 (3%)	15 (3%)	2 (3%)	$p = 0.71$
Neuromediated syncope	12 (2%)	12 (2%)	0 (0%)	$p = 0.27$
Hospital interventions				
CT-scan	527 (82%)	474 (82%)	53 (90%)	$p = 0.11$
Ultrasound scan	150 (23%)	133 (23%)	17 (29%)	$p = 0.31$

(Continued)

TABLE 2 (Continued)

Variables[1]	Total	Survivors	Nonsurvivors 2 days	*p* value and effect size[2]
Surgery	41 (6%)	35 (6%)	6 (10%)	$p = 0.22$
Coronary/neurovascular interv.	57 (9%)	54 (9%)	3 (5%)	$p = 0.28$
Hospital outcomes				
Inpatients	458 (72%)	400 (81%)	58 (98%)	$p < 0.001$* (0.19) ^{S}
Hospitalization days (inpatients)	7 (3–14)	8 (5–15)	1 (1–2)	$p < 0.001$* (0.54) ^{M}
Intensive care unit	149 (23%)	113 (19%)	36 (61%)	$p < 0.001$* (0.29) ^{S}
Mortality				
Day 28	132 (21%)	73 (13%)	–	–
EWS analyzed				
mSOFA	2 (1–5)	2 (1–4)	9 (7–11)	$p < 0.001$* (0.43) ^{S}
SOFA	1 (0–4)	1 (0–3)	7 (6–9)	$p < 0.001$* (0.41) ^{S}

[1]Values expressed as a total number (fraction) and medians (1st quartile-3rd quartile) as appropriate. Bracketed numbers indicate 95% confidence interval. [2]The *p* values were calculated with the Mann–Whitney U test and Chi square test. Effect Size were calculated with the Rosenthal r test [Trivial ^{T} (< 0.2); Small ^{S} (0.2–0.5); Moderate ^{M} (0.5–0.8) and Cramer V test [Trivial ^{T} (< 0.1); Small ^{S} (0.1–0.3); Medium ^{M} (0.3–0.5)]. SpO2, Oxygen saturation; SaFi, pulse oximetry saturation/fraction of inspired oxygen ratio; CT-scan, computerized axial tomography. SOFA, Sequential Organ Failure Assessment; mSOFA, modified Sequential Organ Failure Assessment. *$p < 0.05$.

follow a normal distribution. Additionally, for quantitative variables, effect sizes (ES) were calculated with the Rosenthal *r* test and classified according to the following parameters: trivial (<0.2); small (0.2–0.5); moderate (0.5–0.8); large (0.8–1.3); and very large (≥1.3). For qualitative variables, ES was calculated with the Cramer V test and classified according to the following parameters: trivial (<0.1); small (0.1–0.3); medium (0.3–0.5); and large (≥0.5).

The score discrimination was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the score in a validation cohort. The results from this analysis included the *p* value of the hypothesis test (H0: AUC = 0.5) and the 95% confidence interval (CI). Further statistical characteristics, such as the positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, odds ratio, and diagnostic accuracy, were determined. Additionally, a calibration curve analysis was used to assess the reliability of the results.

All analyses were performed with XLSTAT BioMED software for Microsoft Excel version 14.4.0 (Microsoft Inc., Redmond, WA, USA) and IBM SPSS Statistics version 20.0 (IBM Corp., Armonk USA). In all tests, a confidence level of 95% and a *p* value below 0.05 were considered significant.

3. Results

Between 1 January 2019 and 31 August 2022, we recorded a total of 640 adult patients with neurological disease who were referred to the EDs of the five participating hospitals. Figure 1 shows the flowchart.

The median age was 67 years (IQR: 52–81 years), and 44% (281 patients) were females. The main reasons for medical check-up were seizures (186 cases, 29%), ischemic stroke (127 cases, 20%) and hemorrhage (118 cases, 18%), and their priority of care according to hospital triage was mainly level 2 (43%) or level 3 (41%). In total, 458 patients were hospitalized (72%), and ICU admission was required in 149 cases (23%). The mortality of the patients ranged from 9% (59 cases) within 2 days to 21% (132 cases) within 28 days (Table 2). The comparison of clinical variables between survivors and nonsurvivors showed that patients who died within 2 days presented higher mSOFA and SOFA scores. Supplementary Tables 1, 2 show the comparison of clinical variables for the other two outcomes.

Figure 2 shows the discriminative power of the score for 2-day mortality, revealing a higher AUC for mSOFA (0.925 [95% CI: 0.878–0.972]) than for SOFA (0.902 [0.850–0.955]). Conversely, for 28-day mortality and the need for ICU admission, the SOFA score presented the largest AUC values at 28-day mortality: AUC of 0.875 [95% CI: 0.835–0.915]; and for ICU admission: AUC of 0.845 [95% CI: 0.804–0.886]. The results were supported by those resulting from the calibration curves (Figure 3), showing a better fit of mSOFA for 2-day mortality and a better fit of SOFA for ICU admission and 28-day mortality. Further details of the discriminative power can be found in Table 3.

4. Discussion

In this multicenter prospective cohort study, we analyzed the role of SOFA and mSOFA in the prediction of 2-day and 28-day mortality, as well as the requirement for ICU admission in a cohort of patients with acute neurological pathology, both showing excellent predictive value. However, some differences exist between them, with mSOFA being better for short-term mortality and SOFA for medium-term mortality and ICU admission prediction.

Both scores present a clear difference regarding their use. On the one hand, SOFA is a widespread and consolidated score that, although developed in 1996 to assess the prognosis of patients with sepsis-related multiorgan dysfunction (19), currently has 7 modifications according to the review conducted in 2023 by Xuesong Wang et al. (20) and numerous uses. On the other hand, mSOFA is a modern score scarcely implemented since it was developed in 2021. However,

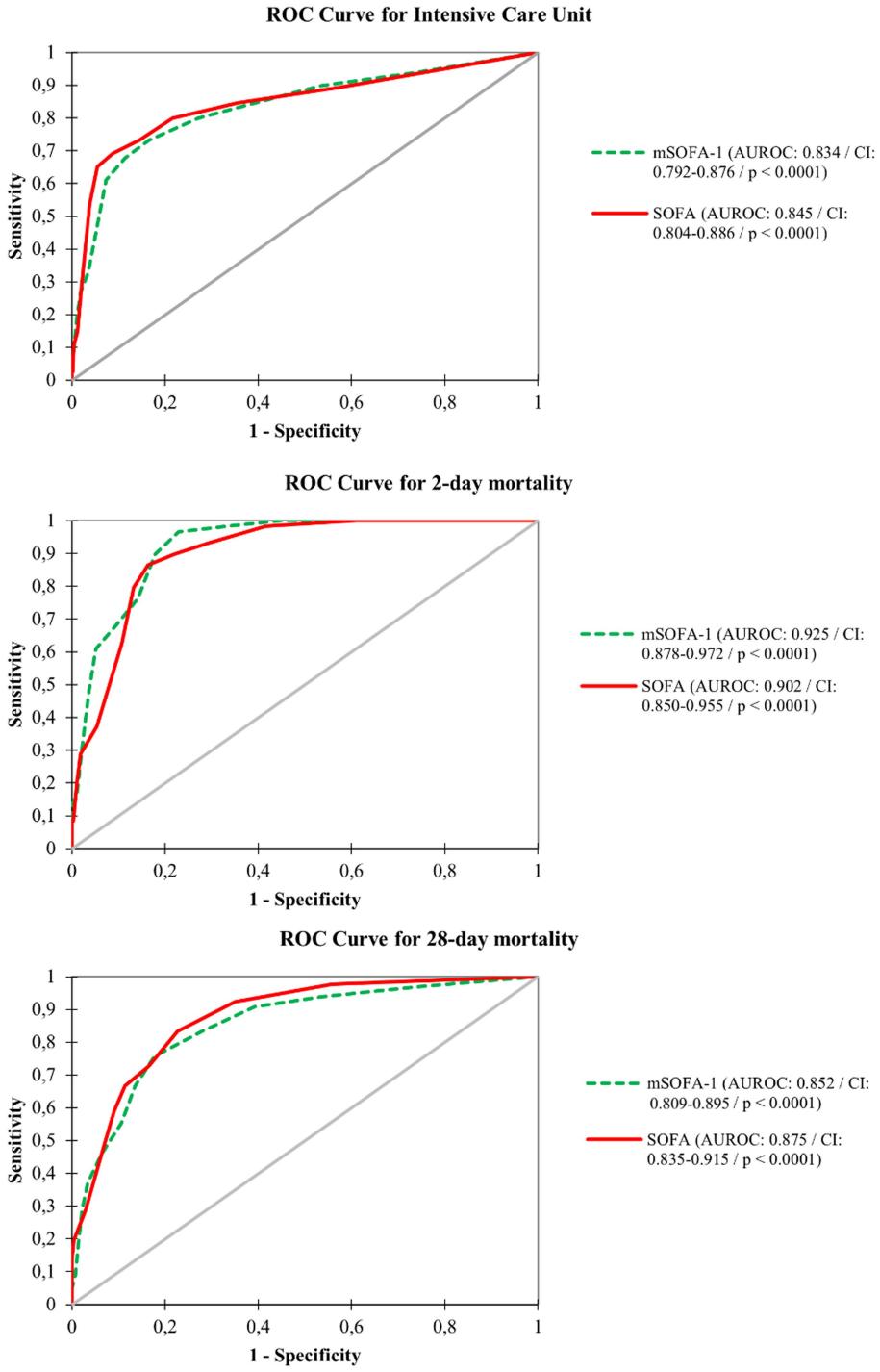

FIGURE 2
Diagnostic performance curves and areas under the curve for intensive care unit, two-day mortality and 28-day mortality. SOFA, Sequential Organ Failure Assessment; mSOFA, modified Sequential Organ Failure Assessment.

several studies have presented its clinical utility. mSOFA was used in an out-of-hospital setting in patients treated by emergency medical services, and the authors found an AUC of 0.946 for predicting 2-day mortality (all-cause) (14). Similar results for predicting 2-day mortality were found in the study by Castro Portillo et al. (21) (AUC = 0.943), which showed that mSOFA performed better than the other four scores: the TIMI risk index (TIMI), the modified shock index (MSI), the Cardiac Arrest Risk Triage (CART) and the National Early Warning Score 2 (NEWS2) for predicting 90-day mortality (in that study, the cohort was patients with acute cardiovascular disease). The study by Melero-Guijarro et al. (22) found that, in addition to 2-day mortality (AUC = 0.877), mSOFA was the best tool for

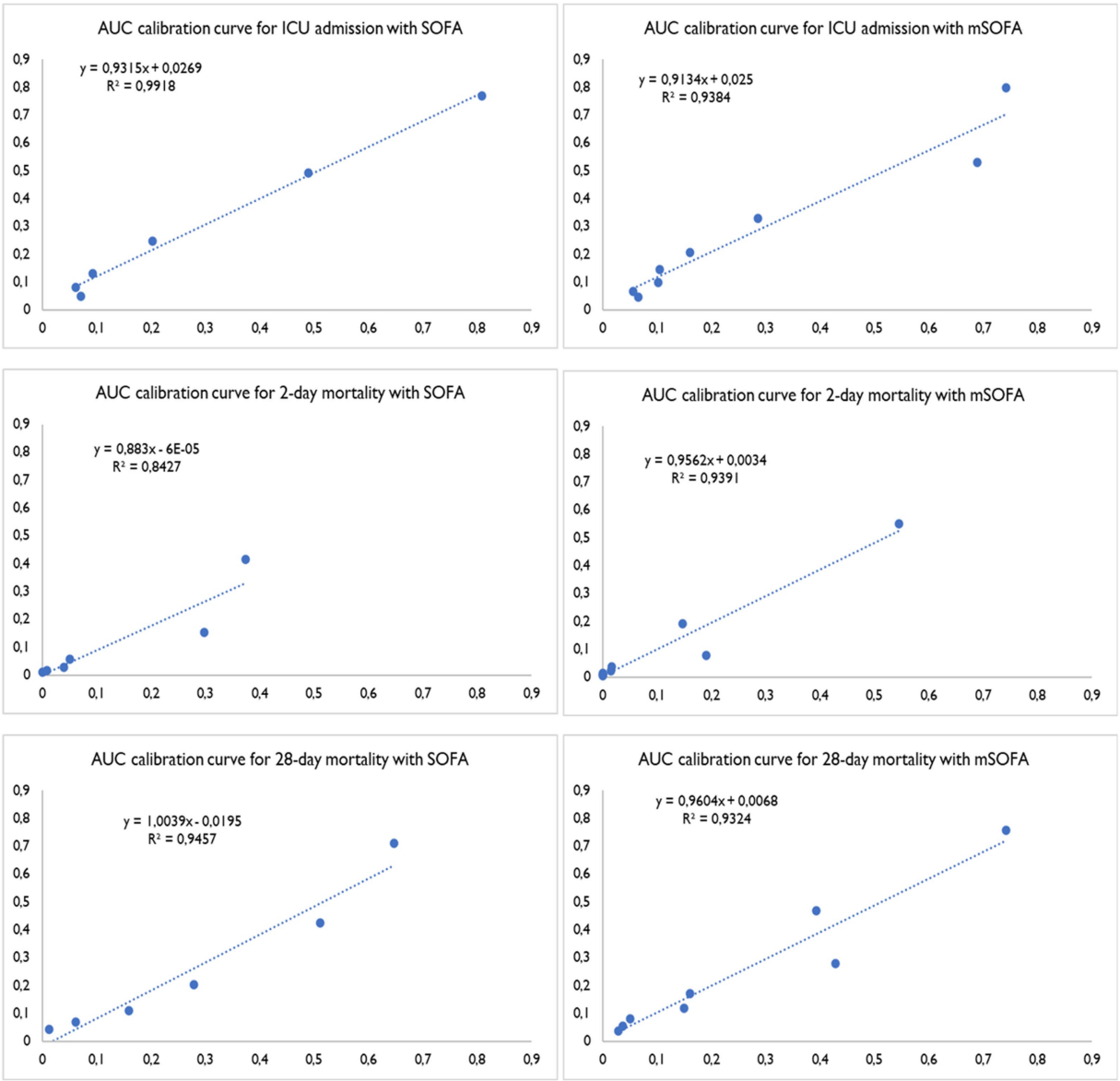

FIGURE 3
AUC calibration curves for intensive care unit care, two-day mortality and 28-day mortality. SOFA, Sequential Organ Failure Assessment; mSOFA, modified Sequential Organ Failure Assessment.

predicting sepsis and septic shock (*vs* NEWS2 and qSOFA). Other works have compared SOFA with other mSOFA versions. One of them, in which mSOFA included hepatic and neurological SOFA criteria and information regarding chronic kidney disease and breathing support, showed that mSOFA performs similarly to SOFA (23). Another study in which mSOFA measured all the parameters from SOFA without the analytical parameters but including the pulse oximetry saturation/fraction of inspired oxygen ratio also performed similarly to SOFA (24).

As explained above, in the score calculation, SOFA and mSOFA have common items, including variables for neurological, cardiovascular, respiratory, and renal function assessment. Regarding the differences, SOFA is focused on coagulation and liver function through analysis of platelets and bilirubin in the laboratory. mSOFA adds lactate, a quick biomarker of anaerobic metabolism and a very specific predictor of poor short-term prognosis. This difference, which in fact could explain our results, supports the use of mSOFA in time-dependent pathologies with early deterioration and SOFA in clinical conditions with unexpected development.

This difference is important in the evaluation of neurological patients, since those patients commonly presented worse outcomes than patients with other conditions. Neurological conditions are generally time-dependent clinical situations in which rapid assessment, transfer, and intervention can be vital; these factors influence the characteristics of the score selected, not only in out-of-hospital care (25, 26) but also during the follow-up of their evolution (27, 28). The choice of an appropriate score is essential, as in some cases, they can be extremely sensitive to changes in the clinical condition (29). For instance, there is wide evidence in the literature of the use of EWS in conditions with a higher associated mortality, such

TABLE 3 AUROC, cutoff points for combined sensitivity and specificity with best score (Youden's test) for the different scores analyzed.

Scores	Nonsurvivors 2 days	Intensive care unit	Nonsurvivors 28 days
mSOFA			
Cutoff	5	5	5
AUROC	0.925 (0.878–0.972)	0.834 (0.792–0.876)	0.852 (0.809–0.895)
Sensitivity	96.6 (88.5–99.1)	73.2 (65.6–79.6)	75.8 (67.8–82.3)
Specificity	77.1 (73.5–80.3)	83.5 (80.0–86.5)	82.3 (78.7–85.4)
PPV	30.0 (23.9–36.9)	57.4 (50.3–64.2)	52.6 (45.6–59.6)
NPV	99.6 (98.4–99.9)	91.1 (88.1–93.4)	92.9 (90.1–94.9)
Likelihood ratio +	4.22 (3.61–4.94)	4.43 (3.55–5.53)	4.28 (3.46–5.28)
Likelihood ratio –	0.04 (0.01–0.17)	0.32 (0.24–0.42)	0.29 (0.22–0.40)
Odds ratio	96.00 (23.13–398.46)	13.79 (8.94–21.28)	14.51 (9.17–22.96)
Diagnostic accuracy	78.9 (75.6–81.9)	81.1 (77.9–83.9)	80.9 (77.7–83.8)
SOFA			
Cutoff	5	5	3
AUROC	0.902 (0.850–0.955)	0.845 (0.804–0.886)	0.875 (0.835–0.915)
Sensitivity	86.4 (75.5–93.0)	69.1 (61.3–76.0)	83.3 (76.1–88.7)
Specificity	83.6 (80.4–86.4)	91.2 (88.4–93.4)	77.4 (73.5–80.8)
PPV	34.9 (27.7–43.0)	70.5 (62.7–77.3)	48.9 (42.4–55.4)
NPV	98.4 (96.8–99.2)	90.7 (87.8–92.9)	94.7 (92.1–96.5)
Likelihood ratio +	5.29 (4.29–6.52)	7.89 (5.82–10.71)	3.68 (3.08–4.40)
Likelihood ratio –	0.16 (0.08–0.31)	0.34 (0.26–0.43)	0.22 (0.15–0.32)
Odds ratio	32.61 (14.99–70.94)	23.33 (14.61–37.24)	17.09 (10.34–28.25)
Diagnostic accuracy	83.9 (80.9–86.5)	86.1 (83.2–88.6)	78.6 (75.3–81.6)

Bracketed numbers indicate 95% confidence interval. SOFA, Sequential Organ Failure Assessment; mSOFA, modified Sequential Organ Failure Assessment; AUROC, area under the receiver operating characteristics; PPV, positive predictive value; NPV, negative predictive value.

as ischemic stroke or hemorrhage (15, 16, 30, 31). However, EWS also has no repercussions in pathologies whose recovery is associated with a restoration of clinical constants, such as seizures (32).

For these reasons, it is important that health professionals deepen their knowledge about tools to assess the clinical status of patients. This allows them to make evidence-based decisions according to the pathology identified. We consider that mSOFA, applied to neurological patients, who commonly present severe conditions, allows a global overview of patient status. In fact, the elevated discriminative power not only allows a proper tagging of patients at risk of deterioration but also, based on the recognition of patients with low risk, allows mSOFA to be used as a decision tool for patient admission. Moreover, the good identification of patient prognosis, evaluated here by the 28-day mortality outcome, allows an adequate selection of the follow-up protocol of patients.

5. Limitations

This study has several limitations that should be considered when interpreting the results. First, the sample selection was not random, and the data were not blinded, which can lead to bias in data selection. This point was minimized by having a multicentered sample and sufficiently clear inclusion criteria so that the opinion of the data extractor did not influence the final sample. In addition, the diagnosis of the clinical condition of acute neurological pathology was based on hospital anamnesis and on the clinical indicators recorded. Second, approximately 70% of the clinical cases studied corresponded to patients with seizures, ischemic stroke or hemorrhage, which limits the possible extrapolation of the results. Third, the study was carried out between 1 January 2019 and 31 August 2022, which means that the COVID-19 pandemic interfered with data collection, and the results obtained could have been affected. Fourth, dynamic evaluation of patient variables allows a better follow-up of patients; unfortunately, informatization of our EMS is not a reality, and therefore, we cannot benefit from the dynamic evaluation of patients. Fifth, although the study included a sufficient multicenter sample to obtain preliminary results, it would be beneficial to carry out additional studies on a wider score and in multiple centers to generalize the findings. Finally, the study reported a considerable percentage of seizures. This type of patient presents hyperacute values and parameters (e.g., lactate) in prehospital critical care, which should be interpreted with prudence. On the other hand, mortality in patients with seizures is usually low but not nonexistent; in fact, it tends to be higher when associated with other pathological conditions. In future studies, it may be pertinent to differentiate the outcomes in this particular cluster.

6. Conclusion

In summary, the results of this study present SOFA and mSOFA as adequate scores that should be considered for the prediction of 2-day and 28-day mortality (all-cause), as well as for ICU admission,

in patients with acute neurological conditions. In particular, mSOFA should be considered when dealing with short-term outcomes, and SOFA should be considered for mid-term and ICU admission. The inclusion of these scores could improve early risk deterioration assessment and patient treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available upon reasonable request by the corresponding author.

Ethics statement

The studies involving humans were approved by Ref. CEIC 2049, MBCA/dgc, PI 18–895, Ref. CEIm PI010-18, PI 2018 10–119. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MD-C: Conceptualization, Data curation, Funding acquisition, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. AS-G: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BP-L: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing. CMM: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – review & editing. CDF: Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. LM-M: Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – review & editing. AM-M: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing. RC-S: Conceptualization, Data curation, Project administration, Resources, Validation, Visualization, Writing – review & editing. MO-A: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. CJ-S: Formal analysis, Investigation, Project administration, Resources, Software, Supervision, Visualization, Writing – review & editing. JM-C: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. FM-R: Validation, Writing – original draft, Writing – review & editing, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1264159/full#supplementary-material

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Machine learning-based clinical decision support for infection risk prediction

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Background: Healthcare-associated infection (HAI) remains a significant risk for hospitalized patients and a challenging burden for the healthcare system. This study presents a clinical decision support tool that can be used in clinical workflows to proactively engage secondary assessments of pre-symptomatic and at-risk infection patients, thereby enabling earlier diagnosis and treatment.

Methods: This study applies machine learning, specifically ensemble-based boosted decision trees, on large retrospective hospital datasets to develop an infection risk score that predicts infection before obvious symptoms present. We extracted a stratified machine learning dataset of 36,782 healthcare-associated infection patients. The model leveraged vital signs, laboratory measurements and demographics to predict HAI before clinical suspicion, defined as the order of a microbiology test or administration of antibiotics.

Results: Our best performing infection risk model achieves a cross-validated AUC of 0.88 at 1 h before clinical suspicion and maintains an AUC >0.85 for 48 h before suspicion by aggregating information across demographics and a set of 163 vital signs and laboratory measurements. A second model trained on a reduced feature space comprising demographics and the 36 most frequently measured vital signs and laboratory measurements can still achieve an AUC of 0.86 at 1 h before clinical suspicion. These results compare favorably against using temperature alone and clinical rules such as the quick sequential organ failure assessment (qSOFA) score. Along with the performance results, we also provide an analysis of model interpretability via feature importance rankings.

Conclusion: The predictive model aggregates information from multiple physiological parameters such as vital signs and laboratory measurements to provide a continuous risk score of infection that can be deployed in hospitals to provide advance warning of patient deterioration.

KEYWORDS

healthcare-associated infection (HAI), machine learning, clinical decision support (CDS), model interpretability, pre-symptomatic infection risk

Background

Healthcare-associated infection (HAI), also referred to as nosocomial infection, remains a significant risk for hospitalized patients and a significant burden on healthcare systems. It has been reported that approximately 1 in 31 hospital patients develop an HAI on any given day (1), and nearly 99,000 people in the U.S. die annually from HAIs (2). Recent data shows that the incidence of HAI's increased during the pandemic (2020) revealing the fragile nature of interventions aimed at prevention (3). Over the last decade, the CDC has developed guidelines and strategies for the prevention of HAIs, focusing on improving clinical practice and antibiotic stewardship. While this guidance has shown some utility in lowering the incidence across several types of HAI, improving the outcomes for those who become infected remains challenging, particularly for the critically ill.

Early detection of *de-novo* infectious disease is critical for improving the outcomes of infected patients (4, 5), for the timely implementation of control measures critical to preventing its spread (6), and for reducing substantial healthcare costs associated with preventable HAIs (7). Hospitalized patients suffering from influenza, up to 20% of whom are nosocomial in origin, have better outcomes when treated with antiviral agents immediately after symptoms present (8). Antibiotic treatment has also been shown to be more effective in producing better outcomes for sepsis patients when administered early in the progression of the infection, particularly for mechanically ventilated patients (4, 5).

Clinical decision support (CDS) tools have received a great deal of attention over the last decade, including those focused on the detection of infection (9–11). Many of these CDS tools are rule based and developed through physician consensus and guidelines. These include more standardized solutions like the acute kidney injury (AKI) eAlert that has been deployed in hospitals in Wales (12, 13) and the National Early Warning Score (NEWS) that is standard for detecting general clinical deterioration in the United Kingdom (14). While these approaches benefit from clinician experience, they are simplified to remain generalizable and fail to capture the complete clinical context required to discriminate difficult or atypical cases. In addition, these approaches are not easily tailored or adapted, for example, to specific patient populations. More recently, several studies have suggested data-driven approaches to create physiological risk prediction algorithms, including in the areas of infection and sepsis prediction (9, 15–17).

This study uses machine learning applied on large retrospective hospital datasets to develop a clinical decision support (CDS) algorithm for the early detection of infection in hospitalized patients. By aggregating information across demographics and a set of 163 vital signs and laboratory measurements, we find our best-performing model can achieve a cross-validated AUC of 0.88 at 1 h before clinical suspicion and maintains an AUC >0.85 for the 48 h period prior to clinical suspicion of infection. By distilling the model down to a set of 36 most frequently measured vital signs, laboratory measurements and demographics, we can still maintain an AUC of 0.86 at 1 h before clinical suspicion. In the results, we further contrast our models against established clinical scoring systems—quick sequential organ failure assessment (qSOFA), and against tracking individual vital signs alone (e.g., temperature, etc.).

Abbreviations: HAI, Healthcare-associated infection; CDS, Clinical decision support; qSOFA, Quick sequential organ failure assessment; SHAP, Shapley additive explanations; Spec, Specificity; TNR, True negative rate; AUC, Area under the ROC curve.

Methods

Description of data

We combined clinical data from three large hospital datasets: the MIMIC-III (Medical Information Mart for Intensive Care III) database comprising deidentified health-related data from patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012 (18), the eICU dataset from Philips' electronic ICU telemedicine business populated with deidentified patients' data from a combination of many critical care units throughout the continental United States between 2003 and 2016 (19), and a dataset of deidentified electronic medical records from patients who stayed in critical care units or low-acuity settings such as general wards in Banner Health collected from 2010 to 2015. In total, the combined dataset includes over 6.5 million patient encounters collected from more than 450 hospitals. Supplementary Figure S1 indicates the types of data present in each hospital dataset.

Ethical approval

The MIMIC-III project was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA). Use of the eICU data was approved by the Philips Internal Committee for Biomedical Experiments. Banner Health data use was a part of an ongoing retrospective deterioration detection study approved by the Institutional Review Board of Banner Health and by the Philips Internal Committee for Biomedical Experiments. Requirement for individual patient consent was waived because the project did not impact clinical care, was no greater than minimal risk, and all protected health information was removed from the limited dataset used in this study.

Infection and control cohort extraction

We define infection patients as those who (1) have a confirmed infection diagnosis, and (2) have data indicating clinical suspicion of infection. Patients in the infection cohort were selected as those with confirmed infection diagnoses via ICD-9 and whose timing of clinical suspicion of infection could be localized by a microbiology culture test order. In the cases where more than one microbiology culture tests were ordered during the hospital stay, we used the earliest timing of the orders to mark clinical suspicion of infection for the given patient. Infection patients were then further screened into an HAI cohort if the timing of clinical suspicion of infection occurred at least 48 h after admission.

Patients in the control cohort were selected as those who have neither an infection-related ICD-9 diagnosis code nor any microbiology culture tests ordered. Since the selection criteria

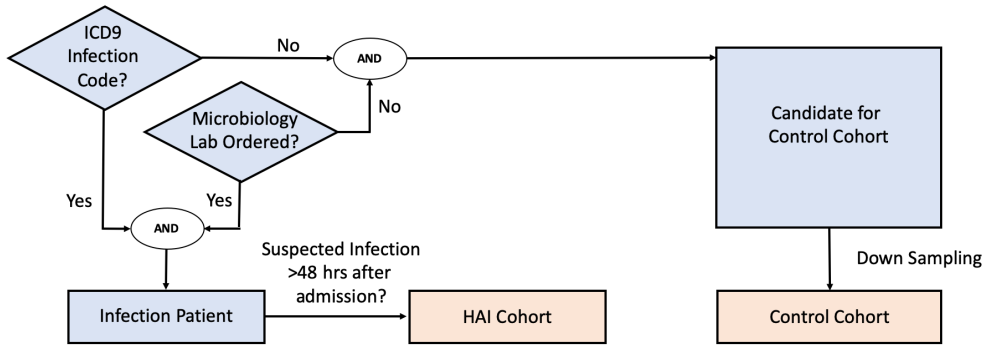

FIGURE 1
Cohort inclusion/exclusion criteria flow diagram.

identified a much larger set of control patients than HAI patients, we randomly down-sampled the control cohort population without replacement to maintain a prior infection odds (prevalence) of 12.5%. This ensured that the training dataset would not be overly dominated by control patients, while still maintaining the HAI cohort as the minority class. Because our machine-learning methodology requires extracting clinical data before clinical suspicion of infection, we generated synthetic event times for the control patients, such that clinical data used for prediction for the control patients could be extracted in the same way as was done for the infection patients. To reduce bias, and to ensure sufficient data prior to event time for model building, we randomly assigned a time-point that is at least 48 h after the control patient's first clinical measurement, and that precedes the end of the control patient's hospital stay as the synthetic event time.

Figure 1 shows the general decision scheme for infection and control cohort extraction. Curation of infection ICD-9 codes is described in detail in the Supplementary material.

For a subset of eICU hospitals, due to limited availability of microbiology interfaces, microbiology charting data was either missing, sporadic, or incomplete. In such cases, the microbiology culture test criterion was replaced with the administration of non-prophylactic antibiotics. The cohort selection was otherwise the same: infection patients were those with at least one administration of non-prophylactic antibiotics and who had at least one ICD-9 code indicating infection, while control patients were selected as those who had neither an ICD-9 code nor any administration of non-prophylactic antibiotics. Clinical suspicion of infection (and screening for the HAI cohort) was then derived using the administration time of first non-prophylactic antibiotics. We validated, in the MIMIC-III dataset, that the two criteria (microbiology culture test versus non-prophylactic antibiotics administration) yield a large overlap of the selected cohorts (see Supplementary material). Extraction of antibiotic records and non-prophylactic labelling details are also described in the Supplementary material.

Description of features and feature subsets used by the models

The extracted features are comprised of three sets of information: demographics (e.g., age, gender, height, weight), vital sign measurements (e.g., heart rate, blood pressure, temperature), and laboratory measurements (e.g., metabolic panels, complete blood count, and arterial blood gas). After feature extraction from each of the three hospital datasets, we applied an extensive preprocessing and cleaning pipeline to create a common and consistent dataset (see Supplementary material). A full list of the features is given in the Supplementary Table S1.

For training our machine learning algorithms, we defined an observation time as 1 h before each patient's clinical suspicion of infection (or randomly assigned event time for control patients). We then extracted the latest measured value of each feature leading up to the observation time and assembled these measurements into a physiological state vector for each patient. This feature vector was then augmented with features characterizing temporal trends from vital sign measurements during the 48 h window preceding the observation time, which was between 49 h before to 1 h before clinical suspicion (or randomly assigned event time for control patients). To mitigate sensitivity to outliers, we applied physiologic plausibility filters to the vital signs measured during the 48 h window before calculating trends. Trend features on laboratory measurements were excluded since they tend to be measured aperiodically (e.g., daily). Vital sign measurements, however, can have temporal resolution as high as every 5 min, e.g., in eICU dataset when data is consistently interfaced from bedside vital signs monitors into eCareManager. We extracted five trend features for the following vital signs: temperature, heart rate, systolic, diastolic, and mean blood pressures, oxygen saturation[1] (SpO_2), and respiration. For example, these trend features for heart rate are:

- Avg. (heart rate): the average heart rate value over a 48 h window.
- Min. (heart rate): the minimum heart rate value over a 48 h window.
- Max. (heart rate): the maximum heart rate value over a 48 h window.
- Var. (heart rate): the variance of heart rate over a 48 h window.
- CoefVar. (heart rate), or CV (heart rate): the coefficient of variation of heart rate over a 48 h window, defined as the standard deviation divided by the mean.

1 Oxygen saturation is predominantly from pulse oximetry measurements and in addition blood gas measurements.

During the validation stage of our algorithm, we additionally applied the classifiers trained on the observation time of 1 h before clinical suspicion to earlier time windows in order to characterize predictive performance over time. These earlier observation times were 6 h, 12 h, 18 h, 24 h, and 48 h before clinical suspicion for infection patients (or randomly assigned event time for control patients). In those instances, we extracted a physiological state vector at earlier observation times in an analogous manner. For example, for the observation time of 6 h before clinical suspicion, we extracted the latest measured value of each feature leading up to 6 h before clinical suspicion and extracted trend features from vital sign measurements during the 48 h window preceding the observation time (that was between 54 h before to 6 h before clinical suspicion). Figure 2 provides a visual summary of the feature extraction pipeline.

Description of algorithms used

We employed two groups of algorithms: (a) linear classifiers, which identify a separating hyperplane in the original feature space; and (b) ensemble-based methods, which iteratively construct a powerful classifier from a set of "weak" nonlinear classifiers. We chose linear classifiers and ensemble-based methods over neural network techniques because we preferred to maintain interpretability of the trained model for clinical deployment, and to minimize the usage of computation resources to enable flexible applications. For linear classifiers we choose logistic regression, and for ensemble methods we benchmarked against abstained adaptive boosting with univariate decision stumps (20) and gradient boosting of decision trees using the XGBoost algorithm (21). Since our dataset is imbalanced in terms of infection prevalence, we employed stratified 5-fold cross-validation, and we did this for each of the three hospital datasets separately: with stratification, both the ratio of control to infection patients, and the ratio of patients from different hospital datasets are maintained in both training and testing sets. We compared model performance of different algorithms using the average model performance from the testing sets of the 5-fold cross-validation. Information about imputation, hyperparameter tuning and performance evaluation is detailed in the Supplementary material.

Description of model interpretation methods

The abstained adaptive boosting algorithm with decision stumps (20) can be expressed as a generalized additive model of the form $R(x) = r_1(x_1) + r_2(x_2) + \cdots + r_p(x_p)$ where $R(x)$ is the composite (ensemble) classifier, $x_1, x_2, \ldots, x_p$ are the p feature inputs, and $r_j(x_j)$, $j = 1, \ldots, p$ are the "weak learner" classifiers learned for each feature. In this case, infection patients are labeled as class 1 (controls are class −1), so that a larger value of $R(x)$ indicates the classifier's stronger confidence of the patient having infection. As a result, each $r_j(x_j)$ can be interpreted as an infection risk function evaluated with respect to a single feature. Because each $r_j(x_j)$ is the weighted sum of decision stumps acting on the respective feature, the infection risk of a single feature is a step function of the feature value, where each step is a decision threshold for different levels of infection risk. In order to control for the impact of feature missingness, we analyzed the relative importance of features through each $r_j(x_j)$ in two ways: (1) *total feature importance*, which evaluates a feature's importance across the entire cohort, and is calculated as the difference in the average infection risk between infection cohort and control cohort from the respective feature; and (2) *adjusted feature importance*, which isolates the feature's contribution on the subset of patients that have the feature measured, and is calculated as the difference in the average infection risk between infection cohort and control cohort that have the respective feature measured. Therefore, *total feature importance* gives an indication of a feature's effectiveness under typical hospital workflow conditions, while *adjusted feature importance* can identify discriminative features despite being less frequently measured.

The gradient boosting algorithm can be interpreted using SHAP (Shapley Additive exPlanations) method (22). SHAP assigns each feature an importance value for a particular prediction, therefore we can compare feature importance by examining the distribution of

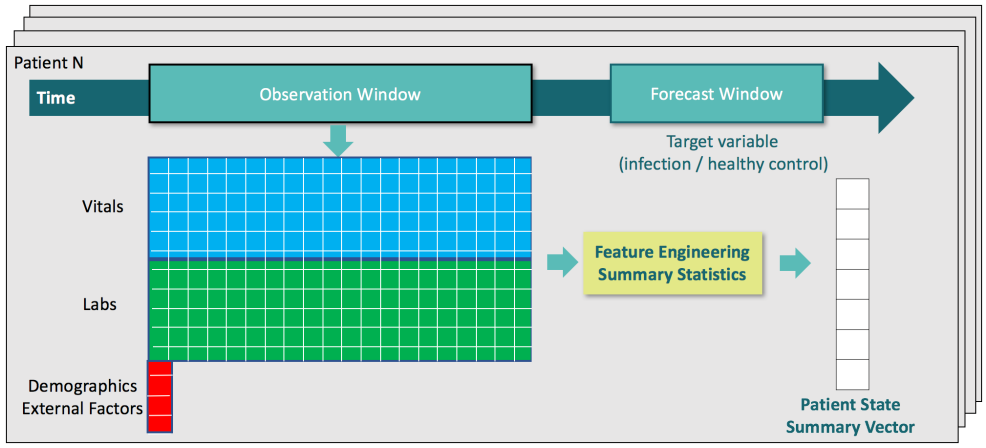

FIGURE 2
Diagram of the feature extraction pipeline.

SHAP values which represent the impacts each feature has on the model output.

Results

The cohort selection criteria resulted in a total training dataset size of 293,109 patients (256,327 control patients; 36,782 HAI patients). Of these patients, 63% are from the Banner Health dataset, 32% are from the eICU dataset, and 5% are from the MIMIC-III dataset. The majority of these patients are treated under ICU or general ward settings. Between the two infection cohort criteria (microbiology culture orders vs. non-prophylactic antibiotics administration), 26,599 HAI patients are identified from microbiology lab and ICD-9 code, while 10,183 infection patients are identified from non-prophylactic antibiotic administration and ICD-9 code.

Model performance

We compared machine learning algorithms in their ability to discriminate infection from control patients using clinical data acquired up to 1 h before clinical suspicion of infection. Our results show that gradient boosting with two level decision trees yielded the best performance with a mean AUC of 0.88 (standard deviation of 0.0009 from 5 testing folds), specificity of 0.93 and sensitivity of 0.54 at the break-even point (where sensitivity is approximately equal to positive predictive value (PPV), see Supplementary material), Sensitivity of 0.80 and 0.64, respectively, for when Specificity is 0.80 and 0.90 (Table 1: Xgboost). This performance was robust with different iterations of randomly down-sampled control cohort (AUC of 0.8839 ± 0.0003; mean ± standard deviation from 5 iterations). Abstained adaptive boosting with decision stump achieved a mean AUC of 0.85, specificity of 0.92 and sensitivity of 0.47 at break-even point, sensitivity of 0.73 and 0.54, respectively, for when specificity is 0.80 and 0.90 (Table 1: Abstained AdaBoost). Logistic regression performs poorly compared with ensemble algorithms, with a mean AUC of 0.77, specificity of 0.91 and sensitivity of 0.40 at break-even point, sensitivity of 0.60 and 0.43, respectively, for when specificity is 0.80 and 0.90 (Table 1: Logistic Regression). These results suggest that ensemble models are superior to linear models in predicting infection.

Next, we asked if ensemble models perform better than established empirical rules and clinical scores in infection prediction. First, fever or high body temperature (>98.6 F) is one of the first symptoms that lead to clinical suspicion of infection. Therefore, we compared temperature measurements between the infection and control cohorts and calculated the discriminative power of temperature at 1 h before clinical suspicion. Temperature by itself has an AUC = 0.59 for detecting infection, which is far inferior to performance achieved with gradient boosting (AUC = 0.88). Second, qSOFA—quick sequential organ failure assessment—was introduced by the Third International Consensus Definitions for Sepsis and Septic Shock task force in 2016, and is proposed as a quick assessment tool for identifying sepsis among patients with infection (23). Based on the Sepsis-3 criteria, we extracted Glasgow Coma Score, Systolic Blood Pressure, and Respiratory Rate from the medical database, and derived qSOFA scores at 1 h before clinical suspicion of infection. In total 111,651 qSOFA scores were extracted, 22,460 from infection cohort and 89,191 from control cohort (infection prevalence = 20.1%). We then calculated the area under ROC curve of infection prediction by using qSOFA alone. qSOFA by itself has an AUC = 0.59 when predicting infection at 1 h before suspicion of infection. To ensure a fair comparison with ensemble models, we re-trained the gradient boosting algorithm using data from the subset of patient cohort that have qSOFA available. Gradient boosting on the patient subset achieves an AUC of 0.83 which is substantially better than the performance of qSOFA. Overall our results suggest advantages of ensemble models over established clinical methods in infection prediction.

We further benchmarked ensemble model performance when feature sets are reduced. First, we excluded all lab measurements and focused on 14 vital signs and demographics factors (plus 50 derived trend features), as they are continuously available and more predictably available than lab measurements. Gradient boosting, re-trained from the feature space excluding labs, achieved a mean AUC of 0.81, specificity of 0.92 and sensitivity of 0.42 at break-even point, sensitivity of 0.62 and 0.45, respectively, for when specificity is 0.80 and 0.90 at 1 h before clinical suspicion of infection (Table 1: GradientBoost—exclude lab). Second, we excluded infrequently measured features that are available for less than 70% of the patient cohort. This produced a reduced feature space with 36 vitals, demographics and laboratory measurements (plus 32 derived trend features). Gradient boosting model, re-trained from frequently measured features, achieved a mean AUC of 0.86, specificity of 0.93 and sensitivity of 0.50 at break-even point, sensitivity of 0.74 and 0.57, respectively, for when specificity is 0.80 and 0.90 at 1 h before clinical suspicion of infection (Table 1: Xgboost—reduced features). These results suggest that it is possible to obtain good performance when reducing the total feature space by half.

In addition, we investigated the infection prediction performance of ensemble models at earlier time points. We applied the most interpretable model (Abstained AdaBoost) and the best performing model (Gradient

TABLE 1 Performance of infection prediction at 1 h before clinical suspicion of infection.

Algorithm	AUC	Sensitivity (spec) break-even point	Sensitivity @ specificity = 0.8	Sensitivity @ specificity = 0.9
GradientBoost	0.884	0.537 (0.934)	0.800	0.635
Abstained AdaBoost	0.852	0.469 (0.924)	0.731	0.536
Logistic Regression	0.772	0.399 (0.914)	0.597	0.431
GradientBoost—exclude lab	0.810	0.415 (0.916)	0.622	0.449
GradientBoost—reduced features	0.862	0.499 (0.928)	0.750	0.574

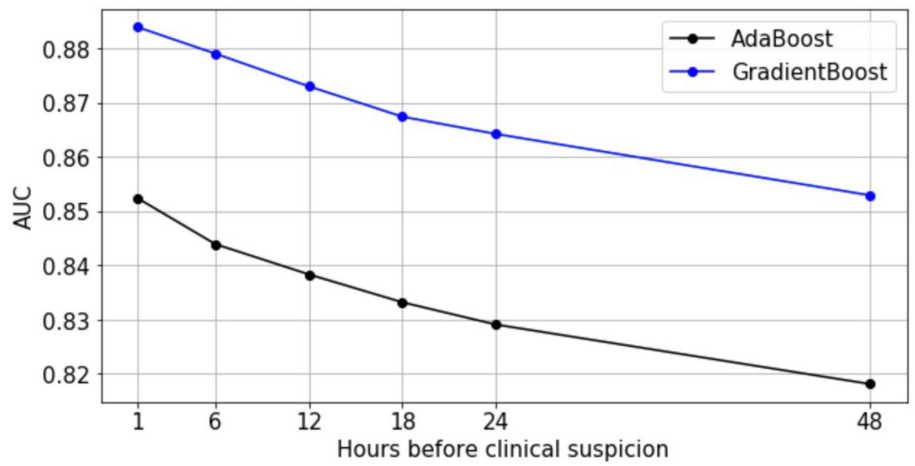

FIGURE 3
Predictive performance of AdaBoost and GradientBoost models relative to time of clinical suspicion.

TABLE 2 Feature importance rankings from abstained AdaBoost model (top 15).

Total feature importance		Adjusted feature importance	
Rank	Feature	Rank	Feature
1	Albumin	1	Albumin
2	Max. (SpO_2)	2	TIBC
3	pH	3	Fibrinogen
4	Min. (SpO_2)	4	Temperature
5	Temperature	5	ESR
6	Avg. (SpO_2)	6	PVRI
7	Var. (SpO_2)	7	Max. (Temperature)
8	Lactate	8	Urinary RBC
9	Bands	9	Avg. (Respiration)
10	Max. (Temperature)	10	WBC
11	Avg. (Respiration)	11	BUN
12	CV (SpO_2)	12	CRP
13	FiO_2	13	Ferritin
14	WBC	14	Neutrophils
15	Bicarbonate	15	Var. (Temperature)

Total feature importance evaluates a feature's importance across the entire cohort; adjusted feature importance isolates the feature's contribution on the subset of patients that have the feature measured.

Boosting) to earlier observation windows to characterize predictive performance over time using the full feature space (Figure 3). Despite degraded model performance over time, gradient boosting maintains an AUC >0.85, while abstained adaptive boosting maintains an AUC >0.81 for 48 h before clinical suspicion. These results support an assertion that it is possible to predict hospital acquired infection earlier, up to 48 h before clinical suspicion of infection.

Model interpretation

To better understand the biomarkers leveraged by the ensemble-based models, we first analyze the AdaBoost algorithm with decision stumps since it is easier to interpret, and then contrast with feature importance scores on the GradientBoost algorithm with decision trees using the SHAP (Shapley additive explanations) method (22).

We first examined the top 15 features ranked by *total feature importance* and *adjusted feature importance* derived from abstained adaptive boosting model trained in the full feature space (Table 2). As described in Methods, *total feature importance* evaluates a feature's importance across the entire cohort, and *adjusted feature importance* isolates the feature's contribution on the subset of patients that have the feature measured. From both metrics, we found that the top 15 features are a mix of laboratory measurements and vital signs. Adjusted feature importance, in particular, identifies discriminative features from laboratory measurements despite being less frequently measured.

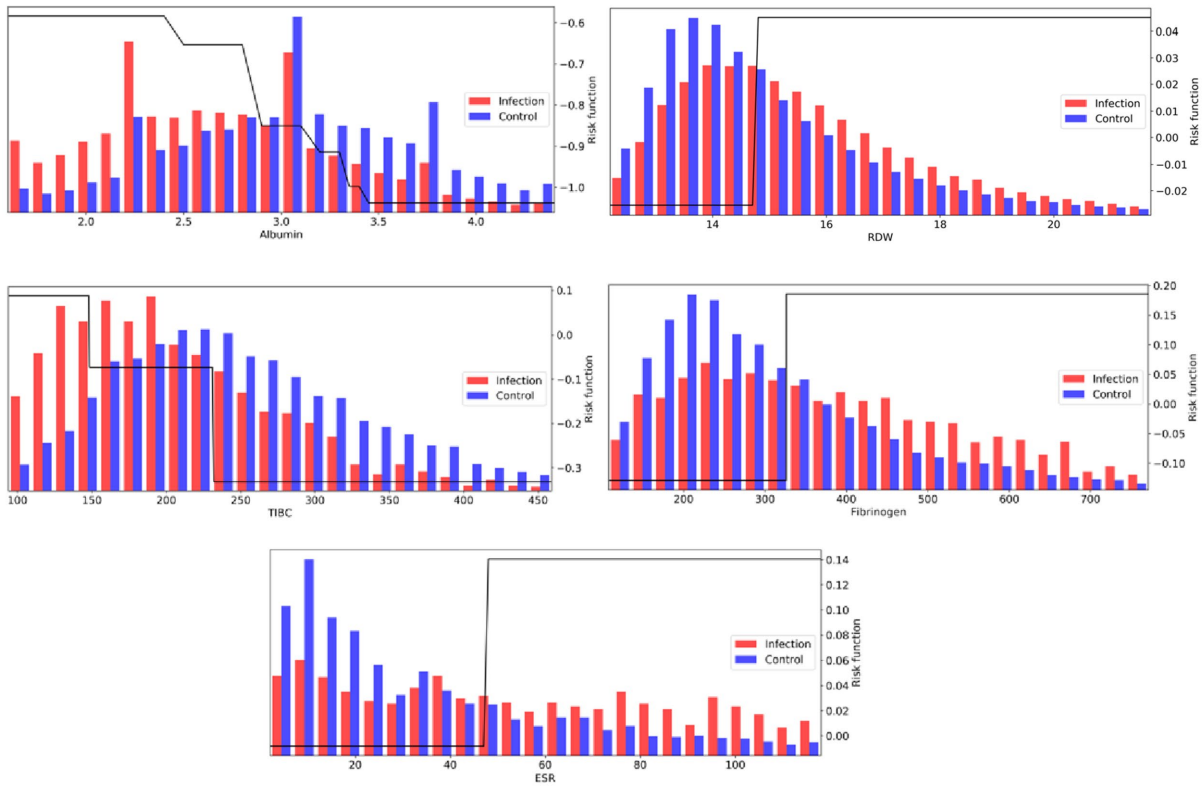

FIGURE 4
AdaBoost risk functions (black) for a subset of the most important laboratory measurements, along with population distribution underlays for infection (red) and control (blue) populations.

The learned risk functions behave in clinically interpretable ways. Figure 4 visualizes the risk functions (black) for a subset of the most important laboratory features, along with population distribution underlays for infection (red) and control (blue) populations. The learned risk functions for these representative features are either monotonically increasing, suggesting that an elevation of the respective clinical measurement is associated with higher infection risk; or monotonically decreasing, suggesting that a decrease of the respective clinical measurement is associated with higher infection risk. During training, each risk function is assembled from a collection of decision stumps that identify key feature thresholds that distinguish levels of infection risk. The scale of the risk function (the *y*-axis in Figure 4 plots) is unitless, but can be used to compare the relative importance of features (see Methods and Table 2 for further details on feature importance).

Amongst laboratory measurements, a number of features associated with, but not necessarily specific to, inflammation were identified. The top feature across both scoring metrics was associated with hypoalbuminemia (low albumin levels <3 g/dL), which has been shown to correlate with inflammation, shock, and sepsis (24). High RDW (>15%) was also a strong biomarker, with literature showing it correlated with inflammation markers CRP and ESR (14). With respect to the *adjusted feature importance* score, a number of infrequently measured features, but highly discriminative, were identified by the model, all of which show associations with inflammatory response: low TIBC (<240 mcg/dL; prevalence = 3%), elevated Fibrinogen (>325 mg/dL; prevalence = 5%), and elevated ESR (>45 mm/h; prevalence = 2%).

Many other laboratory values were also discriminative. Increased risk is identified when Bicarbonate levels fall below approximately 24 mEq/L, which may be indicative of metabolic acidosis, in particular lactic acidosis (elevated Lactate levels above 1.5 mmol/L were also contributing to infection risk). White blood cell concentrations (25) were also strong indicators in the top 15 features, with elevated bands and neutrophil concentrations. Other notable indicators are low HDL and LDL cholesterol levels (26), and increases in blood platelets, which is a sign of host defense and induction of inflammation and tissue repair in response to infection onset (27).

Although laboratory measurements play a significant role, the model also aggregates information from a number of vital signs. The infection risk function based on temperature increases rapidly above 37.8°C, although this accounts for a small percentage of infection patients (5,105 out of 40,406 (~12.6%) of infection patients registered a fever ≥37.8°C at the 1 h window). For controls, 5,579 out of the 96,505 control patients (~5.8%) exhibited a fever ≥37.8C. Infection patients tend to have an elevated heart rate and macro variability, which is reported to be critical for the diagnosis and prognosis of infection by many studies (28, 29). For blood pressure, patients tend to have a decreased blood pressure (systolic, diastolic, and mean), and this effect was often selected by the classifier. Many trend variability features on vitals were selected across temperature, heart rate, blood pressure, oxygen saturation (SpO_2), and respiration, as the infection cohort tends to exhibit a heavier right tail in feature variance measures.

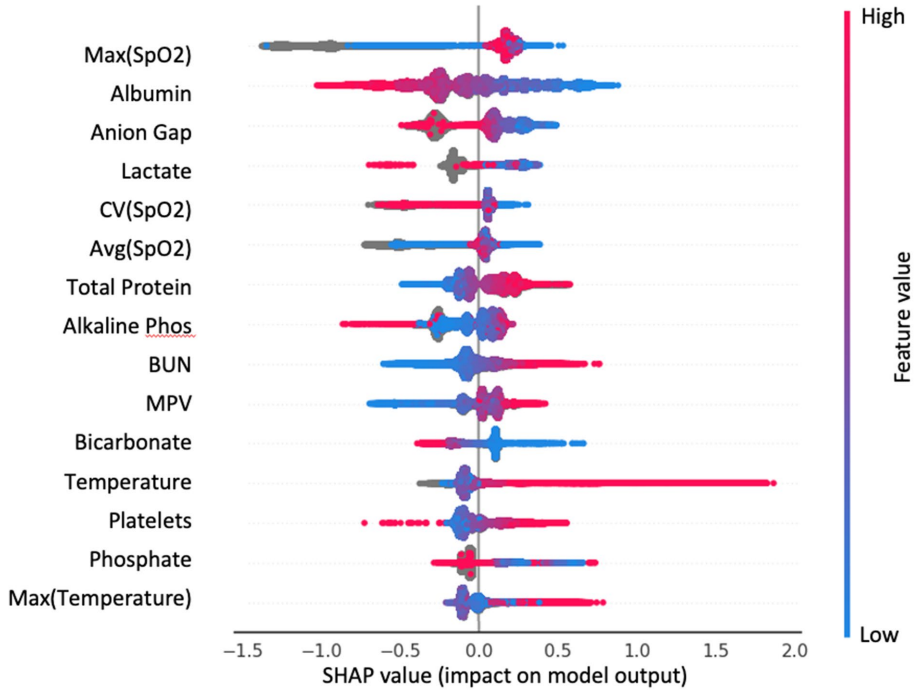

FIGURE 5
Top 15 important features of the GradientBoost model from SHAP analysis. Each dot is a patient; color indicates the value of the feature. SHAP value is on the *x*-axis: large positive value—feature contributes strongly to predict infection; large negative value—feature contributes strongly to predict control.

Changes in vital signs are also reported in the literature to accompany the development of infection (30, 31).

We additionally applied SHAP analysis to extract feature importance rankings from the gradient boosting method (Figure 5). We have observed overlaps in the selected features between the more interpretable AdaBoost model and gradient boosting, such as albumin, SpO_2, bicarbonate, temperature, lactate and BUN.

Algorithm performance on infection subgroups

Patients' host responses to pathogens vary between pathogens and primary sites of infection which result in heterogeneous physiological changes. The extracted HAI cohort is mainly from, ranked by high to low prevalence, the following five infection types (defined by ICD-9 codes—see Supplementary material): pneumonia (17,224 patients), bloodstream infection (12,891 patients), bone/joint/tissue/soft tissue infection (11,613 patients), sepsis (9,643 patients) and urinary system infection (9,118 patients). Note that these patients are primarily from ICUs or general wards, and some patients can have more than one HAI. To compare detection performance on different infection types, we calculated recall (Sensitivity) from the model for patient subgroups of different infection types (Figure 6). We found that the infection model (Table 1: Xgboost) has the highest recall in predicting Sepsis (recall = 0.70) and bloodstream infection (recall = 0.67), followed by pneumonia (recall = 0.61), bone/joint/tissue/soft tissue infection (recall = 0.50) and urinary system infection (recall = 0.46). This result indicates that the infection model performs the best in predicting subgroups of patients that have high acuity.

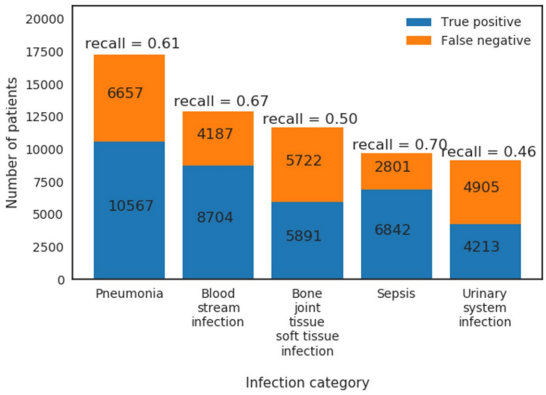

FIGURE 6
True positives and false negatives from GradientBoost model for the top five prevalence infection categories.

Impact of comorbidities on algorithm performance

The previous section assessed true positive rates (recall/sensitivity) for various infection types. By the same token, we may also characterize true negative performance of the algorithm with respect

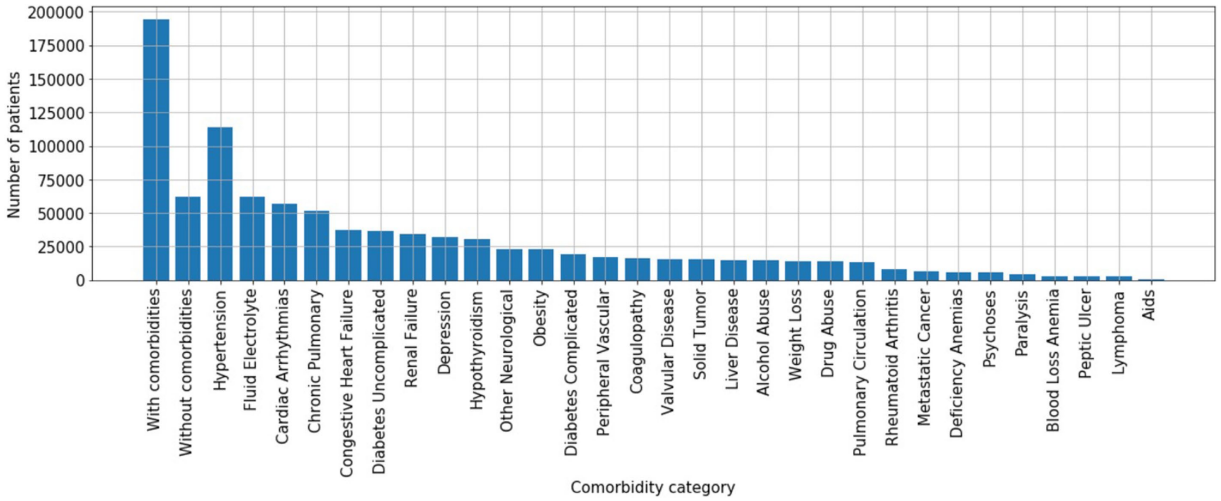

FIGURE 7
Comorbidity prevalence amongst control patients.

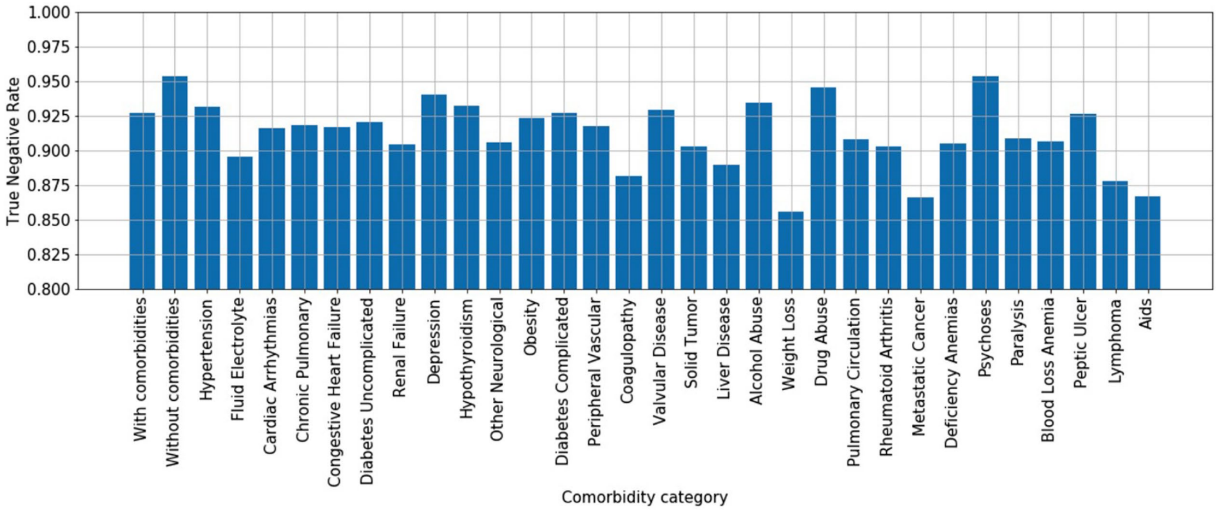

FIGURE 8
True negative rates (specificity) by comorbidity category. *x*-axis: "with comorbidities"—control patients with at least one comorbidity; "without comorbidities"—control patients without any documented comorbidities; 30 comorbidity categories are ordered by prevalence shown in Figure 6 to highlight that the differences in true negative rate are not simple reflections of prevalence.

to various chronic comorbidities exhibited by the control patient population. To do so, we calculated the Elixhauser Comorbidity index (32) for each control patient, which associates diagnostic ICD-9 codes [see Table 2 of (32)] with a set of 30 comorbidity categories. Of the 256,327 control patients, 194,364 (76%) exhibited at least one comorbidity—see Figure 7 for a summary of prevalence of each comorbidity category amongst control patients. We then calculated the infection model's true negative rate (TNR) on the control patient population that exhibited each of the 30 comorbidity categories. In addition, we compared true negative rate for control patients with at least one comorbidity (76% of all control patients, labeled "with comorbidities") to the true negative rate for control patients without any documented comorbidities (24% of all control patients, labeled "without comorbidities")—see Figure 8.

The model performs better at ruling out infection on control patients without comorbidities than those with comorbidities (TNR = 0.95 vs. TNR = 0.925), suggesting that confounding chronic conditions contribute to the false positive rate of the model. Interestingly, with respect to individual comorbidity categories, the model performs best at ruling out infection on control patients with neurological comorbidities (e.g., depression, psychoses), drug/alcohol abuse, and hypothyroidism; presumably since such conditions may have limited overlap in physiological biomarkers related to infection. The worst performing comorbidity categories include fluid/electrolyte

disorders, coagulopathy, weight loss, metastatic cancer, lymphoma, anemia, and AIDS.

Discussion

Our work addresses the fundamental problem of early prediction of HAI, to allow prompt treatment and prevention of infectious disease transmission. We presented a large-scale, retrospective big data machine learning study that provides a data-driven approach to the problem, which can be tailored and adapted to different populations of interest. Infection can be detected by our model with high accuracy in its pre-symptomatic state at 48 h before clinical suspicion.

The training data of 293,109 patients for our infection prediction model was curated from three large hospital datasets that included patient encounters under both high-acuity and low-acuity settings from >400 US hospitals in the span of 16 years. The purpose of using such a large scale dataset for training was to enable the infection prediction model to learn from a heterogeneous patient cohort and to accommodate different data availability and frequencies under different care settings. An extensive preprocessing and data cleaning pipeline was developed to create a common and consistent dataset across the hospitals and acuity settings (see Supplementary material). Because the model was not biased by a single hospital or a single dataset, it should generalize well in real-world use cases in predicting infection.

Ensemble models proved to perform significantly better than both the established empirical rules and clinical scores, and logistic regression, with gradient boosting having the best performance. AdaBoost provided an interpretable model which allows us to map the feature importance to its relevance in clinical literature. For example, multiple laboratory values associated with inflammation ranked high in the feature importance metric, as well as features indicative of acidosis. High heart rate, high temperature and macro variability of vital signs were also indicative of infection, consistently with what has been reported in the literature (28–31). This characteristic of interpretability not only further validates our model, but also provides meaningful information in the clinical setting, quantifying the effect that appropriate action on each of these parameters would have in preventing HAI. It is well known that interpretability of the decision support model is vital to the acceptance of such a predictor in the clinical setting (33).

One important finding of our study is that the high performance of the model is obtained only by aggregating multiple biomarkers. No single "super feature" exists that allows superior classification. This likely reflects at the same time the variable etiology of the HAI—which can be of different natures (respiratory, blood stream infection, sepsis, etc.), the individual variability in the response, and the multi-system nature of the effect of the infection on the patient's physiology. On the other hand, it is still possible to obtain prediction performance that are clinically viable with a reasonable number of clinical measurements. We have showed that with a core set of 36 clinical measurements, the infection model performs at an AUC = 0.86 at 1 h before clinical suspicion of infection.

The algorithm presented in this work could be implemented in a hospital setting by leveraging the existing monitoring systems and infrastructure. When risk of infection is predicted in advance, knowledge of the contributing parameters provided by the transparency of the model would allow secondary assessment and prompt intervention. While the best performing model employs a combination of laboratory test values and vital signs across 163 features, a model trained on 36 of the most frequently measured vital signs, labs and demographics achieves an AUC of 0.86 at 1 h before clinical suspicion. Moreover, a model trained with only vital signs and demographics still achieves an acceptable area under the curve, equal to 0.81. A similar model could be employed in a context that is outside of the hospital (e.g., home monitoring via wearable devices) or in other situations where laboratory values are not easily obtainable.

Limitations

In this section we describe a couple of limitations on our study due to the complex nature of analyzing large retrospective hospital datasets.

First, we tested our model using six different observation times that were 1 h, 6 h, 12 h,18 h, 24 h, and 48 h before clinical suspicion of infection. This design warranted us to have at least an hour of prediction gap before the labeled time of clinical suspicion of infection. This was because determining the exact timing of clinical suspicion of infection was difficult and might not be possible, a prediction gap was built into account for the time differences between the true clinical suspicion of infection and when the culture was ordered in the EMR system. We reasoned in high-acuity settings such as ICUs this 1 h gap was sufficient. For the general ward encounters in Banner dataset, clinical suspicion of infection may arise a couple of hours before the ordering of microbiology culture test given the typical workflow in that environment. In this case it is more accurate to look at the performance at the observation time of 6 h before clinical suspicion instead of 1 h to evaluate the model in predicting infection shortly before the true clinical suspicion of infection (we reported AUC = 0.88 at 6 h before clinical suspicion, Figure 3 blue line).

Second, our infection and control cohort selection criteria were designed to be conservative, in that we only included patients in infection cohort if they satisfied both criteria (ICD-9 and microbiology) and only included patients in control cohort if they met none of the two criteria. This means that we excluded, from the infection cohort, those patients who had an infection diagnosis but whose timing of clinical suspicion of infection could not be localized; and that we excluded, from the control cohort, those patients who had a microbiology culture test ordered but did not have an infection diagnosis. For the latter patient group, some of them may have a negative culture but the culture was ordered based on clinical suspicion. It would be interesting to examine the model performance in those patients. We suspect, because those patients may have overlap in symptomatology (hence the clinical suspicion) and physiological biomarkers related to infection, our model may have a degraded performance in true negative rates in this group of patients.

Finally, the patient encounters used in this study happened before the full adoption of ICD-10 therefore we used ICD-9 to select the infection patients. We understand that ICD-10 have improved granularity over ICD-9 therefore are more specific in identifying health conditions. For training a general infection prediction model where different types of infections were grouped in the same category, we believe the granularity provided in ICD-9 is sufficient. However, it

would be interesting to see how using ICD-10 would affect the model performance in different infection categories (Figure 6).

Conclusion

This study developed an algorithm for early identification of infection in hospitalized patients, using machine learning applied to large retrospective hospital datasets. The model is able to identify patients who are infected with reasonable performance up to 48 h before clinical suspicion of infection (AUC >0.85). The trained models utilize ensembles of decision trees, which are readily interpretable and provide ranked lists of feature importance. The primary model leveraging all available (163) vital signs, laboratory measurements and demographics achieves the best performance; however, a secondary model limited to the 36 most commonly measured clinical measurements still achieves an AUC = 0.86 at 1 h before clinical suspicion. The models compare favorably to established clinical rules and show high potential for real-world hospital deployment as a clinical decision support aid.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: MIMIC-III dataset is available in PhysioNet repository, https://mimic.physionet.org/. A portion of the eICU dataset used in this study is available in PhysioNet repository, https://eicu-crd.mit.edu; the remaining of the eICU dataset is proprietary to Philips. The Banner Health dataset is a proprietary dataset that is not publicly shareable. Requests to access these datasets should be directed to Banner Health and Philips.

Ethics statement

The studies involving humans were approved by the following ethics committee/institutional review board: The MIMIC-III project was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA). Use of the eICU data was approved by the Philips Internal Committee for Biomedical Experiments. Banner Health data use was a part of an ongoing retrospective deterioration detection study approved by the Institutional Review Board of Banner Health and by the Philips Internal Committee for Biomedical Experiments. Requirement for individual patient consent was waived because the project did not impact clinical care, was no greater than minimal risk, and all protected health information was removed from the limited dataset used in this study. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

TF, CK, and BC participated in the study design, data preparation and analysis, machine learning model training, and contributed to writing of the manuscript. DN, SM, CZ, EG, and DM contributed to study design, data analysis, and contributed to writing of the manuscript. DS provided clinical consultation, manuscript review, and interpretation of results. JF provided clinical consultation and participated in hypothesis development, cohort identification, and manuscript review and interpretation of results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

TF, DN, CK, SM, EG, and BC are employees of Philips Research. CZ, JF, and DM were employees of Philips Research. DS is employee of Banner Health.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1213411/full#supplementary-material

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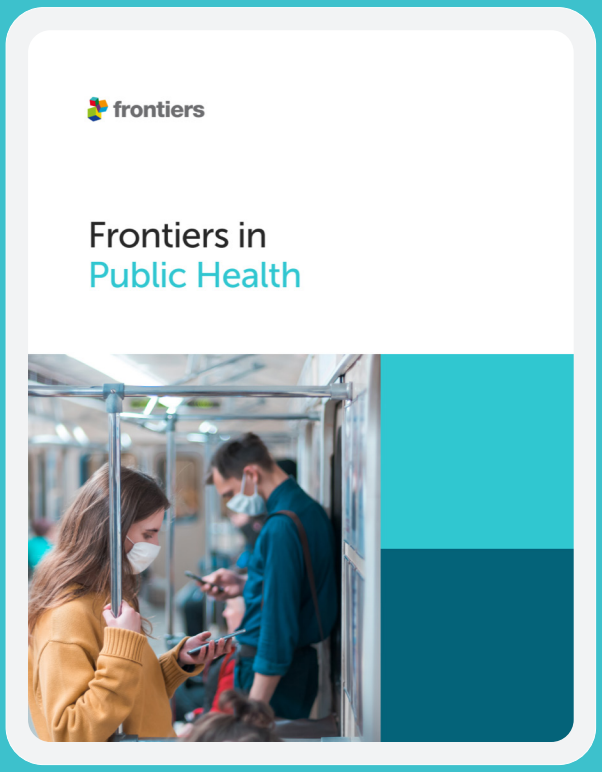

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