**Supplementary**

**Search strategy**

**PubMed**

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Query | Results | Date |
| #1 | ((((CRC[Title/Abstract]) OR colorectal cancer[Title/Abstract]) OR (carcinoma of colon[Title/Abstract] AND rectum[Title/Abstract])) OR (cancer of colon[Title/Abstract] AND rectum[Title/Abstract])) | 119855 | 29-Dec-21 |
| #2 | chemotherapy[Title/Abstract] | 403498 | 29-Dec-21 |
| #3 | #1 AND #2 | 16304 | 29-Dec-21 |
| #4 | Filters:Clinical Trial | 2198 | 29-Dec-21 |

**Embase**

|  |  |  |  |
| --- | --- | --- | --- |
| #1 | 'colorectal cancer':ab,ti OR 'carcinoma of colon':ab,ti OR 'carcinoma of rectum':ab,ti OR 'cancer of colon':ab,ti OR 'cancer of rectum':ab,ti | 168581 | 29-Dec-21 |
| #2 | chemotherapy:ab,ti | 640814 | 29-Dec-21 |
| #3 | #1 AND #2 | 26246 | 29-Dec-21 |
| #4 | #3 AND 'clinical trial'/de | 3366 | 29-Dec-21 |

**List of included studies**

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2. Salehiniya H, Pouyesh V, Tarazoj AA, et al. Colorectal cancer in the world: incidence, mortality and risk factors. Biomedical Research and Therapy. 2017;4(10).

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4. Pinson H, Cosyns S, Ceelen WP. The impact of surgical resection of the primary tumor on the development of synchronous colorectal liver metastasis: a systematic review. Acta Chir Belg. 2018;118(4):203-211.

5. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, Group EGW. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii1-9.

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7. Benson AB, 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22(16):3408-3419.

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17. Mandema JW, Verotta D, Sheiner LB. Building population pharmacokineticpharmacodynamic models. I. Models for covariate effects. Journal of Pharmacokinetics & Biopharmaceutics. 1992;20.

18. Ulrika, Wählby, E., et al. Assessment of Actual Significance Levels for Covariate Effects in NONMEM. Journal of Pharmacokinetics & Pharmacodynamics. 2001.

19. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. The Lancet. 2019;394(10207):1467-1480.

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21. E., Mitry. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. Côlon & Rectum. 2008;2(1):37-39.

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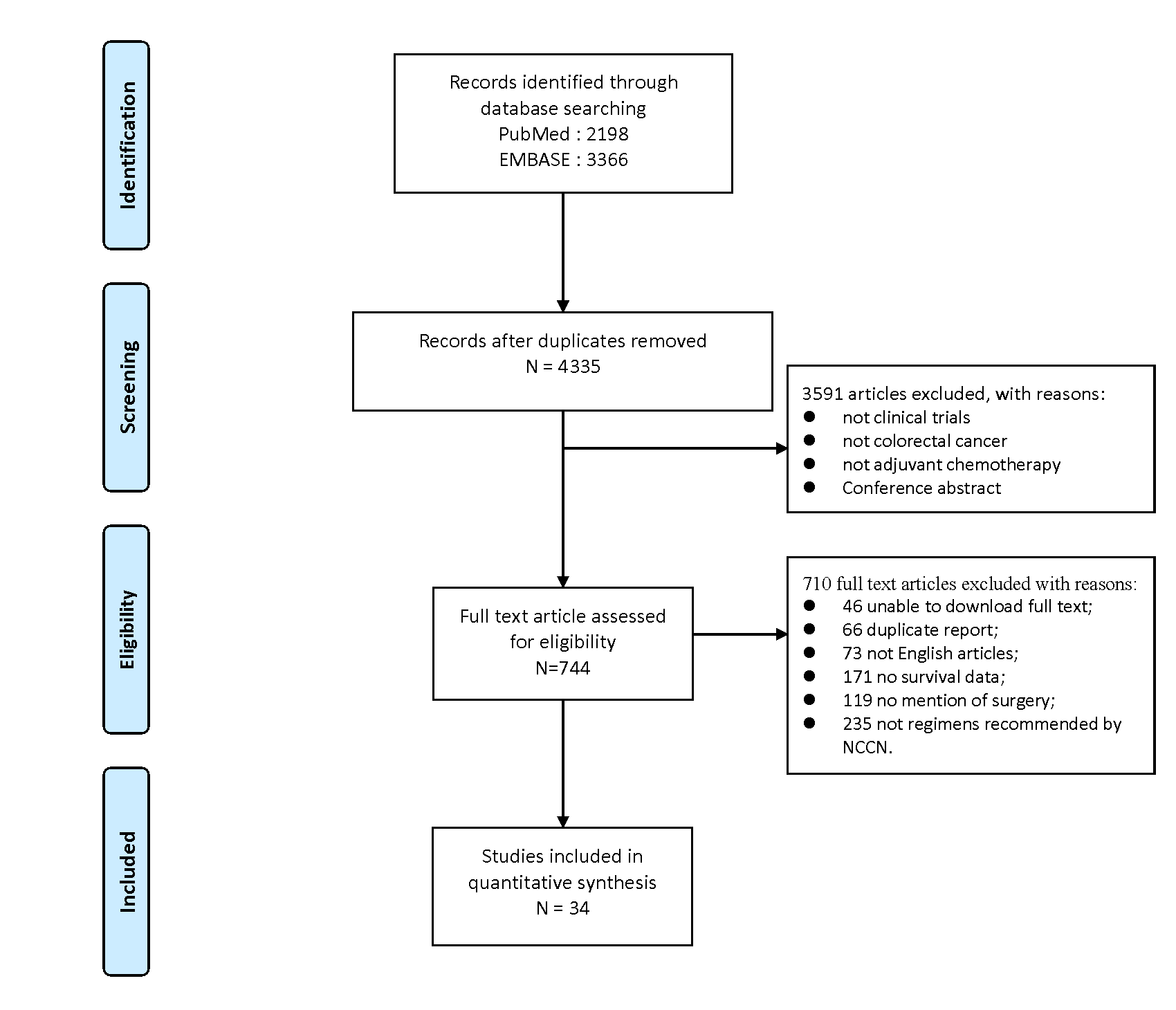
25. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol. 2011;29(28):3768-3774.

26. La Regina D, Mongelli F, Fasoli A, et al. Clinical Adverse Events after Endoscopic Resection for Colorectal Lesions: A Meta-Analysis on the Antibiotic Prophylaxis. Dig Dis. 2020;38(1):15-22.

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**Figure S1.** Flow chart demonstrating the inclusion and exclusion of studies into the analysis. NCCN indicates National Comprehensive Cancer Network.

**Model building**

Parametric survival models were used to analyze survival data, such as OS and DFS, of patients treated with surgery alone and adjuvant chemotherapy after radical surgery. The survival model was related to the hazard function h(t), which can be interpreted as the instantaneous risk of death at moment t. The relationship between the survival model and the hazard function was as follows:

*Survival model* (1)

This study evaluated four different hazard functions as follows:

*Constant* (2)

*Gompertz* (3)

*Weibull* (4)

*Lognormal ,* (5)

In Equations 2–5, h(t) represent the value at risk at time t, and *λ* and *β* denote the risk at moment 0 and the coefficient of risk over time, respectively. h(t) in Equation 5 conforms to the log-normal distribution, where *μ* and *σ* are the median and standard deviation of the log-normal distribution, respectively. The best hazard model was selected based on the minimum value of the objective function, standard error of the model parameter estimation, and goodness-of-fit of the model.

When conditions permit, the inter-trial variation (Equation 6) and residuals (Equation 7) were added to the model parameters to account for differences between observed and model-predicted values. The inter-study variability (η) and residual variability (ε) could be explained by a random effects model (Equation 6–7), where inter-study variability is introduced into the model parameters in an exponential form and residual variability is chosen as an additive model:

(6)

(7)

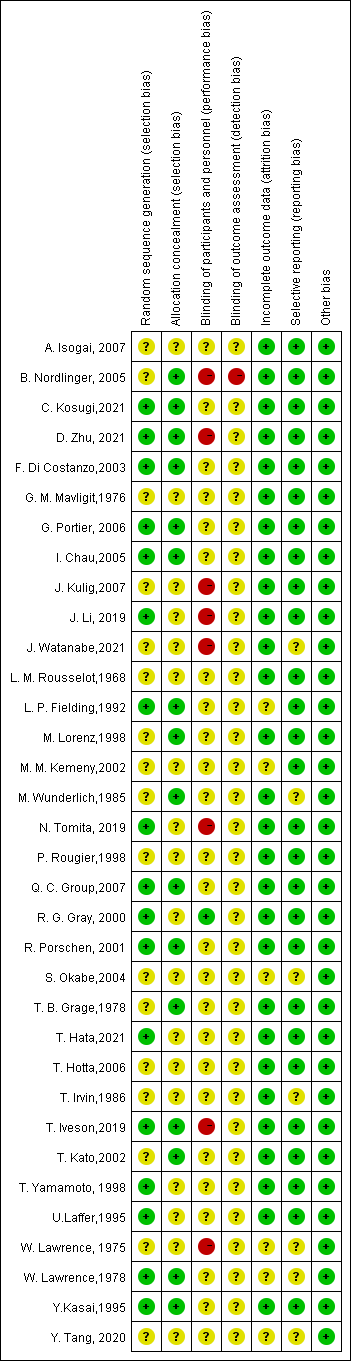
(8)

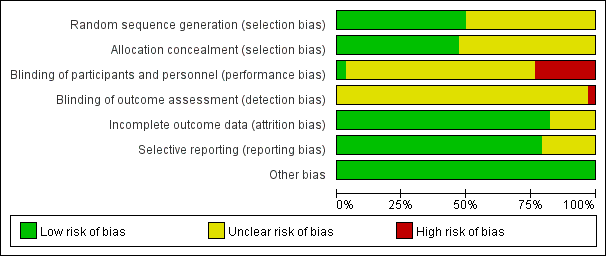
In Equation 6, is the individual value of the model parameter for study i, and is the typical population value of the model parameter. is the within-trial variation of the model parameter, which conforms to a normal distribution with mean 0 and variance ωi2. In Equation 7, is the measured value of survival at time j in study i. is the predicted value of survival at time j of study i. is the residual of time j of study i, which conforms to a normal distribution with mean 0 and variance σ2. is corrected by the standard error of survival at time j of study i (SEj,i), which is considered to be smaller with the decrease in the standard error. The formula for SEi,j is given in Equation 8, where Nj,i is the sample size of time j in study i.

Once the base model was constructed, factors that have a potential impact on the model parameters were examined, including subjects’ age, sex, location of carcinoma *in situ*, Dukes' classification, and the treatment regimen (with or without fluorouracil, with or without fluorouracil combined with calcium folinic acid regimen). When a variable was missing and the proportion of missing values was less than 30%, the median of the remaining studies for that variable was used to replace the missing data. Covariate analysis was not used when the proportion of missing values was greater than 30%. All covariates were introduced into the model in an exponential form, which was multiplied by the hazard function h(t). Forward and backward methods were used to screen the covariates to confirm the covariates that eventually entered the model. The bound of OFV decreasing in the forward method was set at 3.84 (P<0.05), while in the backward method, the bound was set at 6.63 (P<0.01).

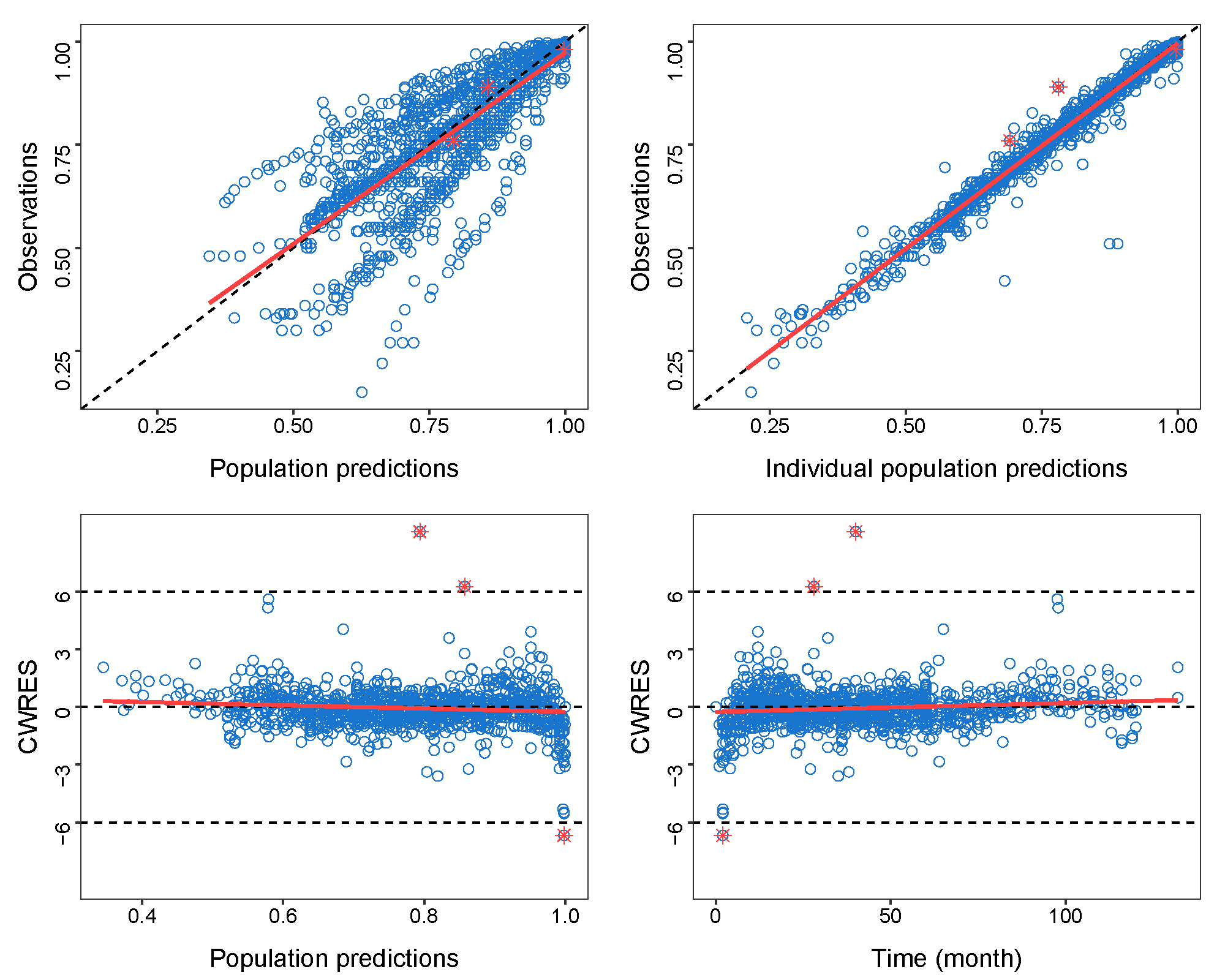
**Table S1.** Summary of included studies. NA: not mentioned.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Treatment** | **Age** | **Male** | **Sample** | **Stage** | **Chemotherapy regimens** | **Surgery** | **Random** | **Blind** |
| **(year, median)** | **(%)** | **size** | **(Yes/No)** | **(Yes/No)** | **(Yes/No)** |
| T. Iveson,2019 | Chemotherapy | 65 | 60.5 | 3044 | Ⅱ/Ⅲ | Capecitabine+Oxaliplatin+FU | Yes | Yes | No |
| Chemotherapy | 65 | 60.6 | 3044 | Capecitabine+Oxaliplatin+FU |
| T. Hata,2021 | Chemotherapy | 68 | 53 | 185 | Ⅱ/Ⅲ | UFT+LV | Yes | Yes | No |
| Chemotherapy | 67 | 56.7 | 188 | UFT+LV |
| A.     Isogai,2007 | Chemotherapy | NA | 55.9 | 34 | Ⅱ/Ⅲ | UFT | Yes | Yes | No |
| SAKK,1995 | Surgery alone | 62 | 53.4 | 266 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 61 | 56.3 | 267 | Mitomycin+FU |
| Y. Kasai,1995 | Chemotherapy | 59 | 48 | 327 | Ⅱ/Ⅲ | 5-FU | Yes | Yes | No |
| Surgery alone | 61 | 52.3 | 279 |  |
| Chemotherapy | 58 | 62.6 | 297 | 5-FU |
| Surgery alone | 60 | 60.1 | 293 |  |
| C. Kosugi,2021 | Chemotherapy | 66 | 69.7 | 80 | Ⅱ/Ⅲ | UFT+LV | Yes | Yes | No |
| Chemotherapy | 65.5 | 65.8 | 79 | UFT+LV+Oxaliplatin |
| T. Yamamoto,1998 | Surgery alone | 60 | 64.9 | 37 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 60 | 60.5 | 38 | 5-FU+LV |
| L. M. Rousselot, 1968 | Surgery alone | NA | 48.1 | 250 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | NA | 53.6 | 81 | 5-FU |
| J. Li, 2019 | Chemotherapy | 61 | 66 | 87 | Ⅰ/Ⅱ/Ⅲ/Ⅳ | XELOX | Yes | Yes | No |
| Chemotherapy | 60 | 62 | 85 | Ⅰ/Ⅱ/Ⅲ | XELOX |
| M.Wunder,1985 | Surgery alone | 64.9 | 50 | 62 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 60.1 | 52.5 | 59 | 5-FU+MMC+ARA-C |
| G. Portier, 2006 | Surgery alone | NA | 62.4 | 85 | Ⅰ/Ⅱ/Ⅲ/Ⅳ |  | Yes | Yes | No |
| Chemotherapy | NA | 53.5 | 86 | LV+FU |
| R. Porschen, 2001 | Chemotherapy | 62.6 | 46.2 | 331 | Ⅱ/Ⅲ | Levamisole+5-FU | Yes | Yes | No |
| Chemotherapy | 62.4 | 42.7 | 349 | 5-FU+LV |
| S. Okabe, 2004 | Chemotherapy | 54 | 65 | 23 | Ⅱ/Ⅲ | CDDP + 5FU + LV | Yes | Yes | No |
| Chemotherapy | 61 | 54 | 28 | 5FU + LV |
| B. Nordlinger, 2005 | Chemotherapy | 64 | 52 | 471 | Ⅰ/Ⅱ/Ⅲ | Levamisole+FU | Yes | Yes | No |
| Chemotherapy | 64 | 58 | 455 | FU + LV |
| Chemotherapy | 63 | 49 | 465 | Levamisole+FU |
| Chemotherapy | 63 | 53 | 466 | FU + LV |
| G. M. Mavligit, 1976 | Surgery alone | NA | NA | 73 | Ⅲ |  | Yes | Yes | No |
| M. Lorenz, 1998 | Surgery alone | 61 | 64 | 111 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 61 | 50.9 | 108 | 5-FU+LV |
| W. Lawrence,1975 | Surgery alone | 63.4 | 47 | 76 | Ⅰ/Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 60.7 | 50 | 80 | 5-FU |
| W. Lawrence,1978 | Surgery alone | NA | NA | 101 | Ⅰ/Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | NA | NA | 102 | FU |
| J. Kulig, 2007 | Surgery alone | 58.9 | 70.5 | 102 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 58.5 | 64.7 | 102 | 5-FU+LV+Irinotecan |
| M. M. Kemeny, 2002 | Surgery alone | 62 | 62.6 | 56 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 59 | 73.3 | 53 | FUDR+5-FU |
| T. Irvin, 1986 | Surgery alone | 66.6 | 49.3 | 67 | Ⅰ/Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 67.5 | 51.5 | 68 | 5-FU |
| T. Hotta,2006 | Surgery alone | NA | 56.3 | 16 | Ⅱ/Ⅲ |  | Yes | No | No |
| Chemotherapy | NA | 61.1 | 36 | l-LV+5-FU |  |  |  |
| P. Rougier,1998 | Surgery alone | NA | 50 | 599 | Ⅰ/Ⅱ/Ⅲ |  | Yes | Yes | No |
| T. Kato, 2002 | Surgery alone | 61.4 | 53.5 | 144 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 60.2 | 53.1 | 145 | UFT |
| Q. C. Group,2007 | Surgery alone | 63 | 60 | 1617 | Ⅰ/Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 63 | 62 | 1622 | l-LV+FU |
| R. G. Gray, 2000 | Surgery alone | 62 | 58.9 | 2434 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | 62 | 59.1 | 2464 | FU+LV |
| Chemotherapy | 62 | 68.1 | 2463 | FU+LV |
| Chemotherapy | 62 | 59.2 | 2429 | FU+levamisole |
| J. Watanabe,2021 | Chemotherapy | 65.5 | 53.3 | 478 | Ⅲ | UFT+LV | Yes | Yes | No |
| Chemotherapy | 65 | 55.1 | 477 | SOX |
| D. Zhu, 2021 | Chemotherapy | 59 | 56 | 347 | Ⅱ/Ⅲ | FU+Oxaliplatin | Yes | Yes | No |
| T. B. Grage, 1978 | Surgery alone | NA | NA | 113 | Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | NA | NA | 98 | 5-FU |
| L. P. Fielding, 1992 | Surgery alone | NA | NA | 145 | Ⅰ/Ⅱ/Ⅲ |  | Yes | Yes | No |
| Chemotherapy | NA | NA | 123 | Heparin |
| Chemotherapy | NA | NA | 130 | Heparin+5-FU |
| F. Di Costanzo, 2003 | Chemotherapy | 63 | NA | 844 | Ⅱ/Ⅲ | 5-FU | Yes | Yes | No |
| Chemotherapy | 63 | NA | 859 | LV+5-FU |
| I. Chau,2005 | Chemotherapy | 62 | 54.5 | 404 | Ⅱ/Ⅲ | 5-FU/LV | Yes | Yes | No |
| Chemotherapy | 63 | 53.2 | 397 | PVI 5-FU |
| Y. Tang, 2020 | Surgery alone | NA | 14.7 | 52 | Ⅰ/Ⅱ/Ⅲ |  | Yes | NA | No |
| Surgery alone | NA | 14.2 | 42 |  |
| N. Tomita, 2019 | Chemotherapy | NA | NA | 654 | Ⅲ | Capecitabine | Yes | Yes | No |
| Chemotherapy | NA | NA | 650 | Capecitabine |

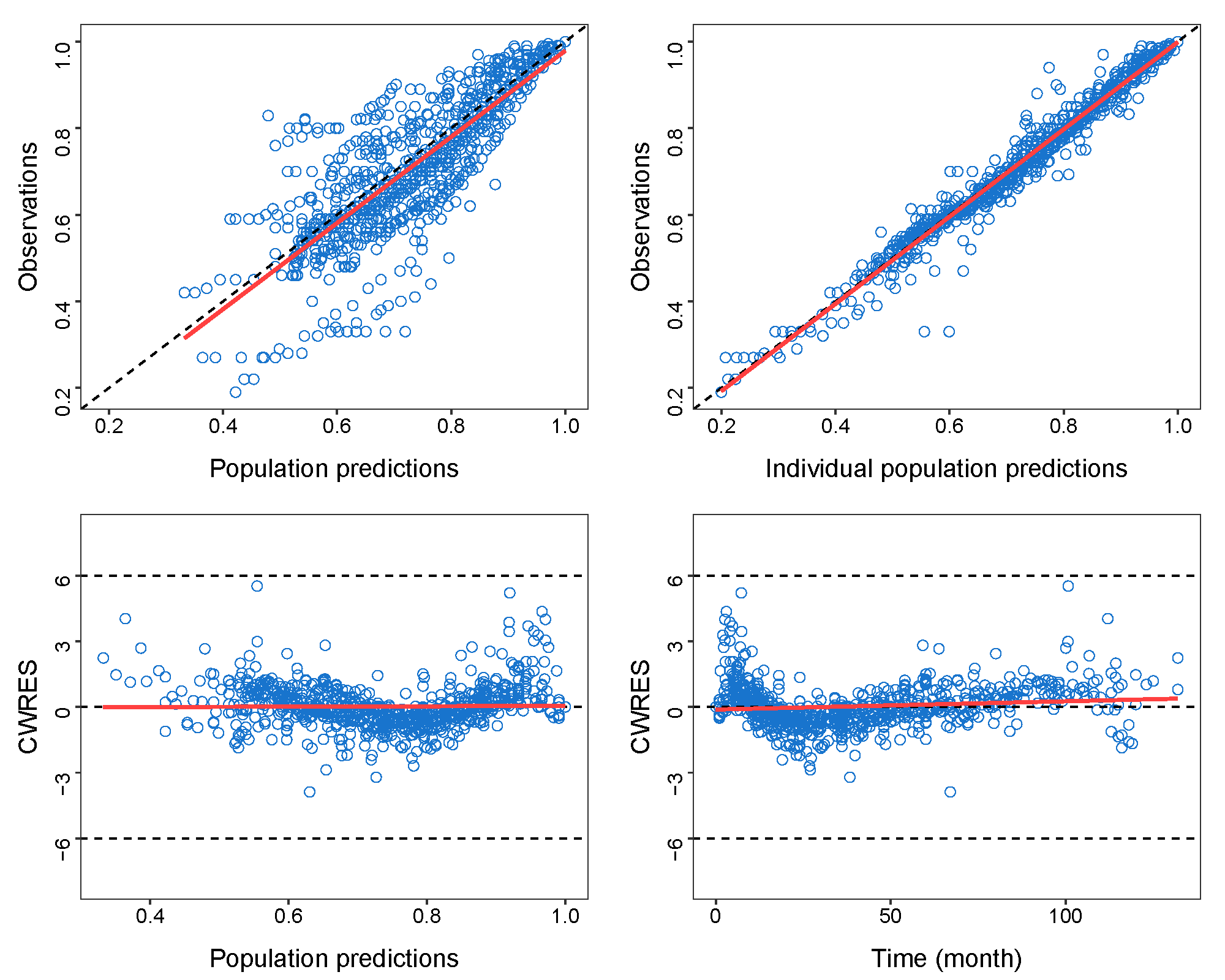


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**Figure S2.** Risk of bias assessment. Using Cochrane’s risk of bias assessment tool to assess the risk of bias. In this tool, studies were deemed to be at high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding, processing of incomplete data, selective reporting, and other biases.

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**Figure S3.** Goodness of fit plot for OS model. (A) Population predicted value versus observed value. (B) Individual predicted value versus observed value. (C) Conditional weighted residuals versus population predicted value. (D) Conditional weighted residuals versus time. The dashed and solid lines in (A) and (B) represent identity and regression lines, respectively, whereas in (C) and (D), the black lines are the position where conditional weighted residual equal 0 and the red lines are the regression lines.

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**Figure S4.** Goodness of fit plot for DFS model. (A) Population predicted value versus observed value. (B) Individual predicted value versus observed value. (C) Conditional weighted residuals versus population predicted value. (D) Conditional weighted residuals versus time. The dashed and solid lines in (A) and (B) represent identity and regression lines, respectively, whereas in (C) and (D), the black lines are the position where conditional weighted residual equal 0 and the red lines are the regression lines.

**Figure S5. Safety analysis**

