

# **Clinical Frailty Scale (CFS) indicated frailty is associated with increased in-hospital and 30-day mortality in COVID-19 patients: a systematic review and meta-analysis**

## **Supplementary material**

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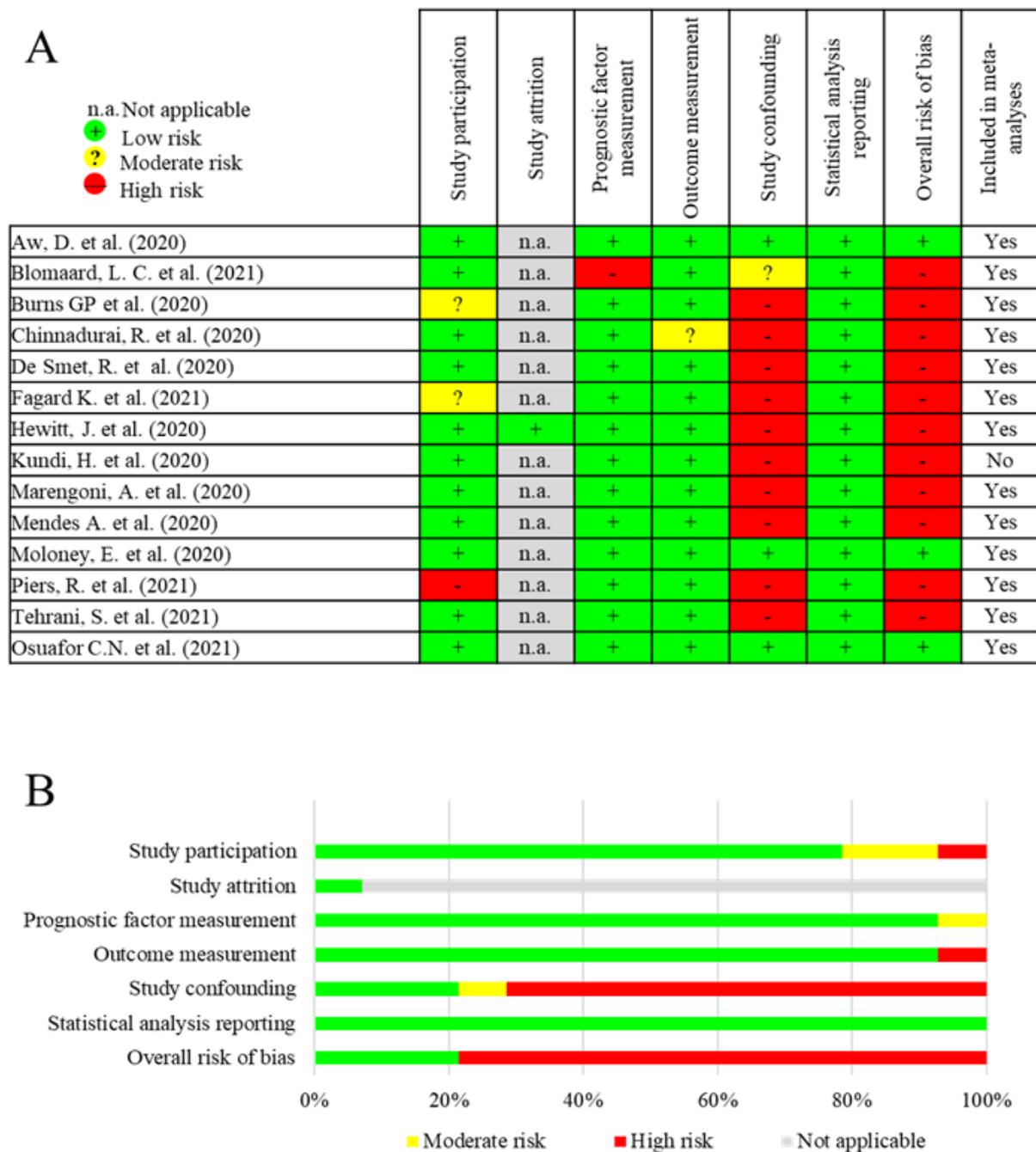
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## Risk of bias assessment

### Risk of bias assessment protocol

Following the recommendations of the Cochrane Collaboration, the Quality in Prognosis Studies (QUIPS) tool was used by MR and TL independently [1]. Disagreements were resolved by ZM. In the study participation domain gender, age, ethnicity and comorbidities were taken into account. Study attrition was not judged for retrospective studies. In the prognostic factor measurement domain, the specification of the frailty assessor, information about their training and missing data on frailty were taken into account. Less than 10% missing data was considered low risk, 10–20% some concerns and more than 20% resulted in high risk for the whole domain. Outcome measurement and statistical analysis domains carried low risk in most cases because mortality is a hard outcome and we mostly used raw data. In case of ICU admission, a detailed protocol for ICU admission was needed. In the study confounding domain, studies reporting baseline information for the frailty groups separately were judged low risk if no clinically significant differences were seen, some concerns if some differences were seen and high risk if no data was reported. The overall risk of bias was calculated using the suggestions of Grooten et al. [2].

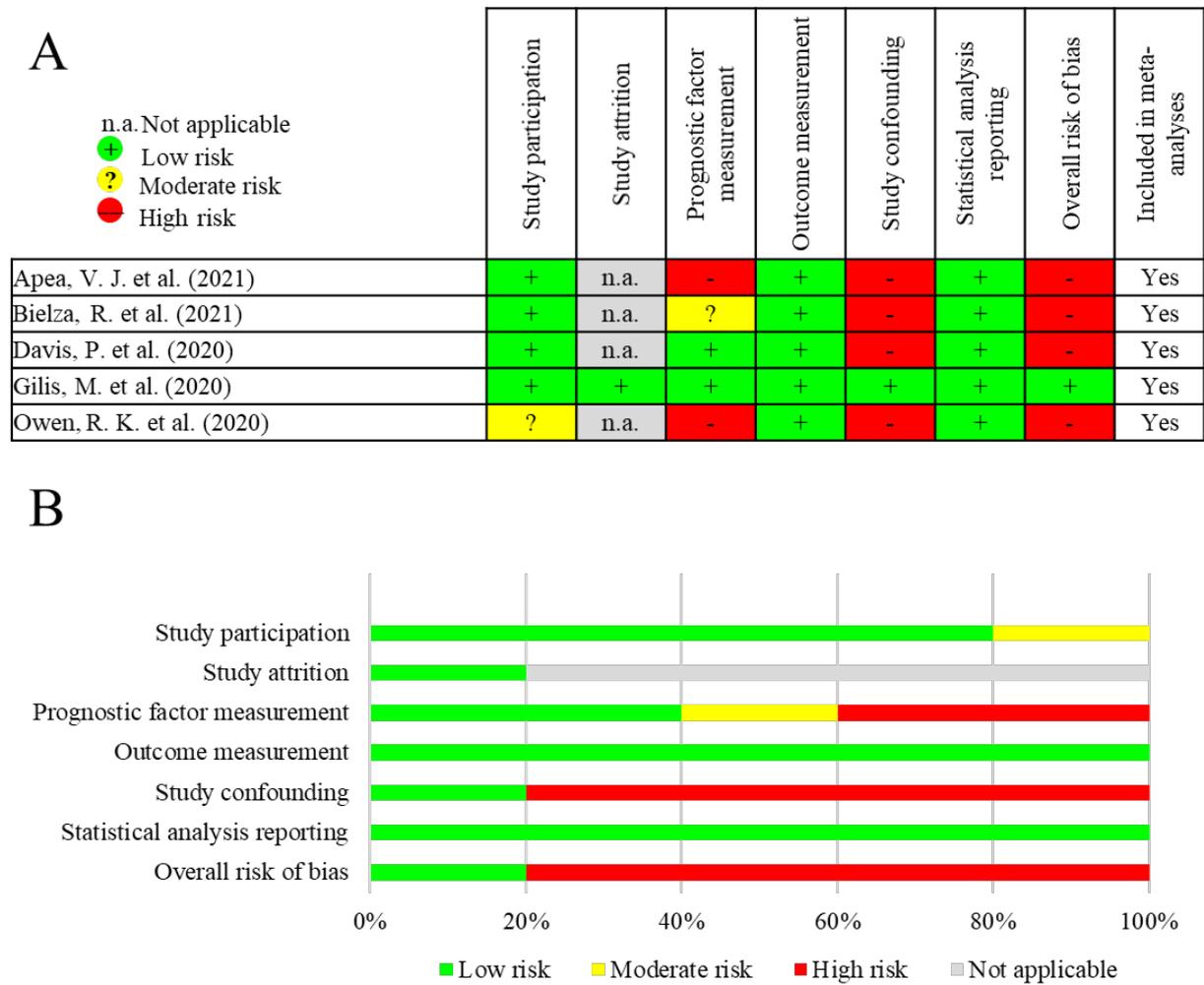
Figure S1 — In-hospital mortality



**Figure S1 Risk of bias assessment on study level [A] and across studies [B] for studies reporting in-hospital mortality in frail versus not frail patients**

For details please see the protocol for risk of bias assessment above.

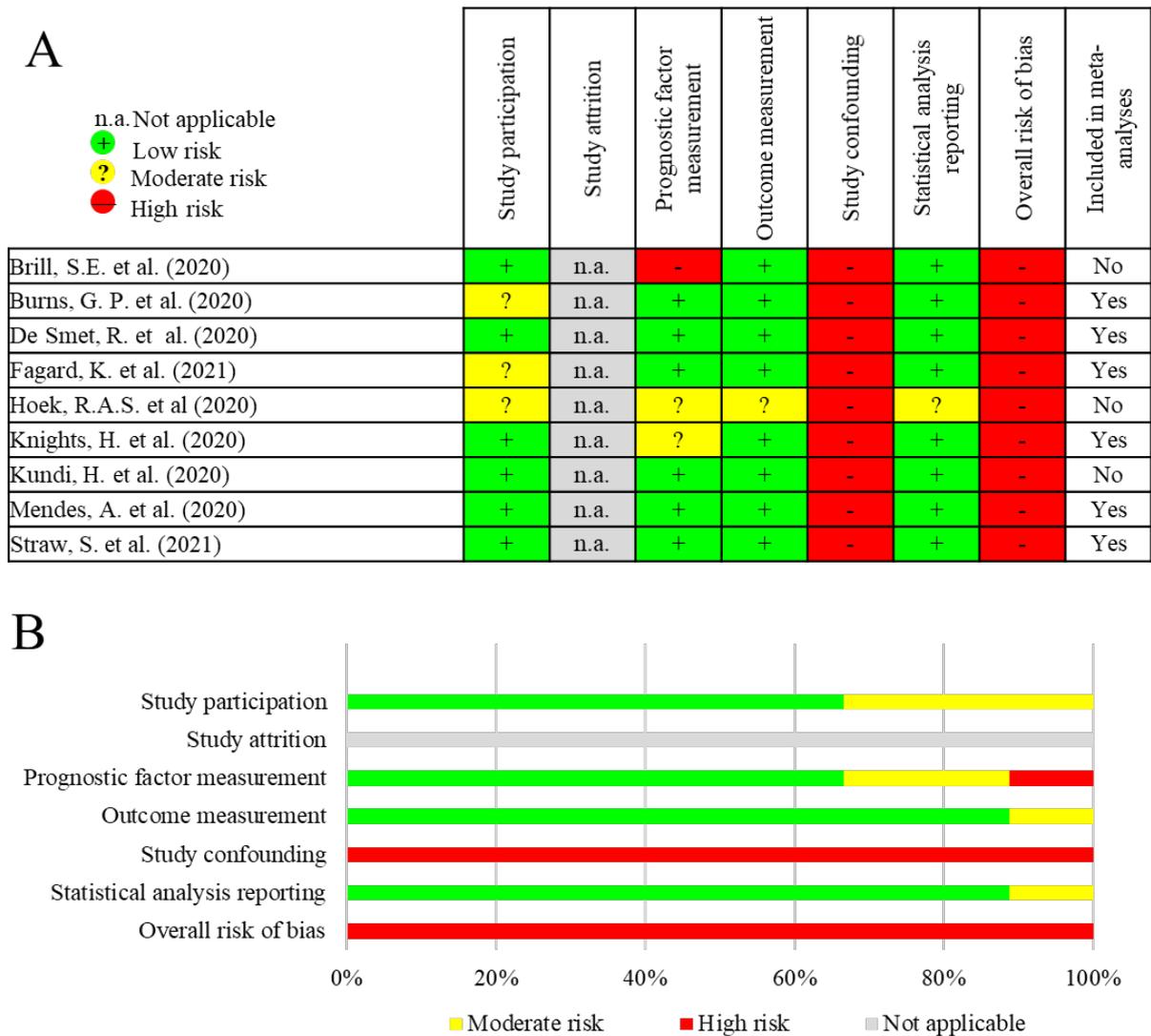
Figure S2 — 30-day mortality



**Figure S2 Risk of bias assessment on study level [A] and across studies [B] for studies reporting 30-day mortality in frail versus not frail patients**

For details please see the protocol for risk of bias assessment above.

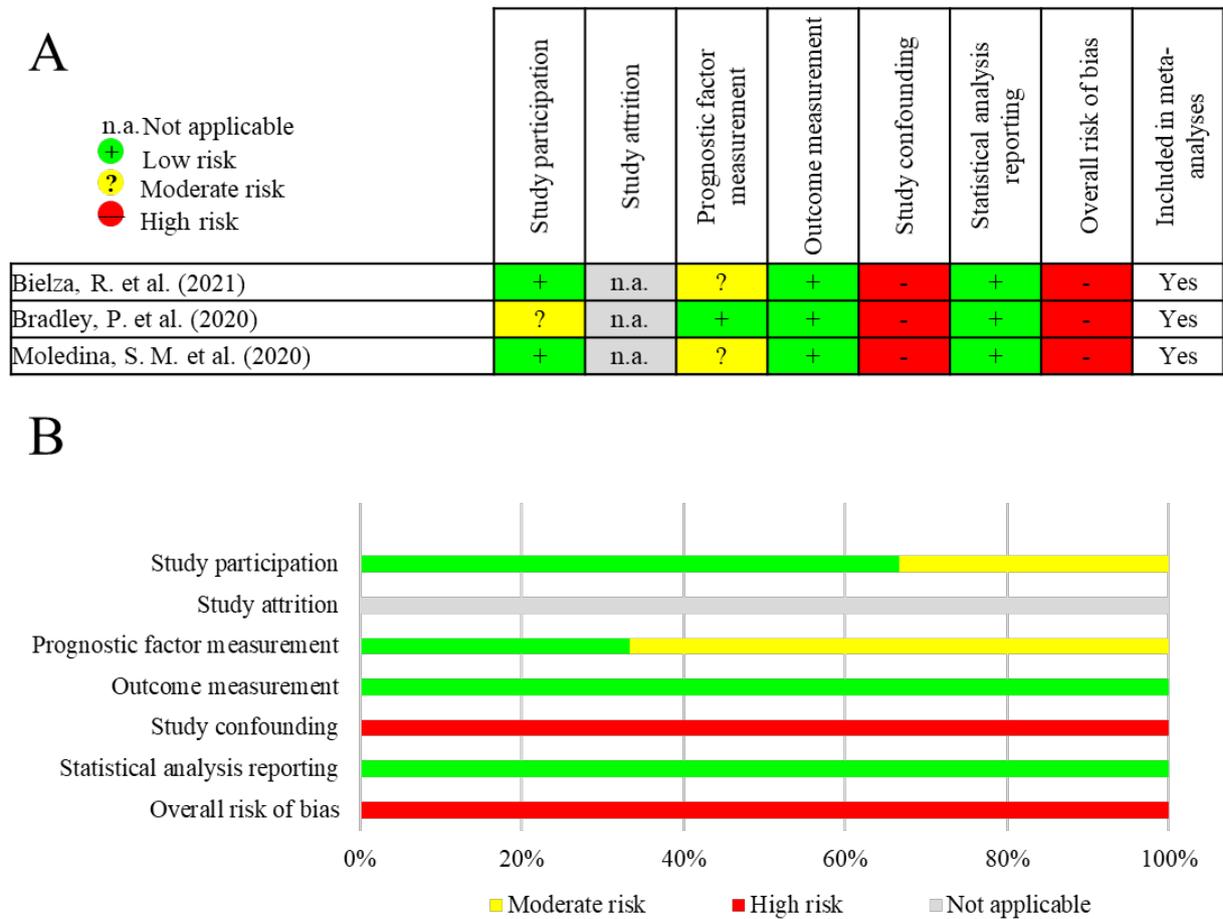
Figure S3 — Average frailty comparing deceased and discharged



**Figure S3 Risk of bias assessment on study level [A] and across studies [B] for studies reporting average frailty comparing discharged and deceased COVID-19 patients**

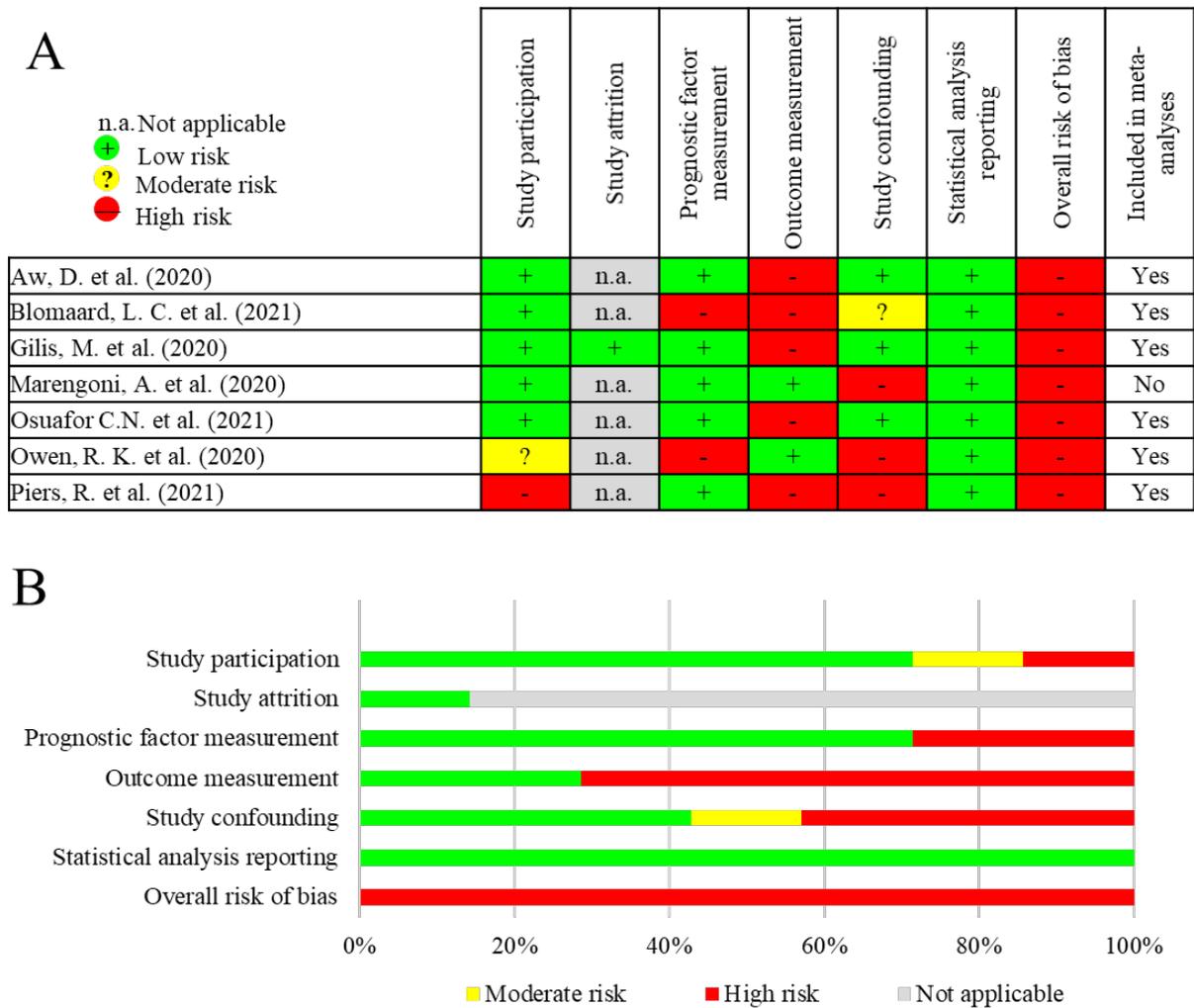
For details please see the protocol for risk of bias assessment above.

Figure S4 — Average frailty comparing survived for 30-days vs died



**Figure S4 Risk of bias assessment on study level [A] and across studies [B] for studies reporting average frailty comparing COVID-19 patients who survived for 30 days and who did not**  
 For details please see the protocol for risk of bias assessment above.

Figure S5 — ICU admission



**Figure S5 Risk of bias assessment on study level [A] and across studies [B] reporting intensive care admission in frail versus not frail patients**

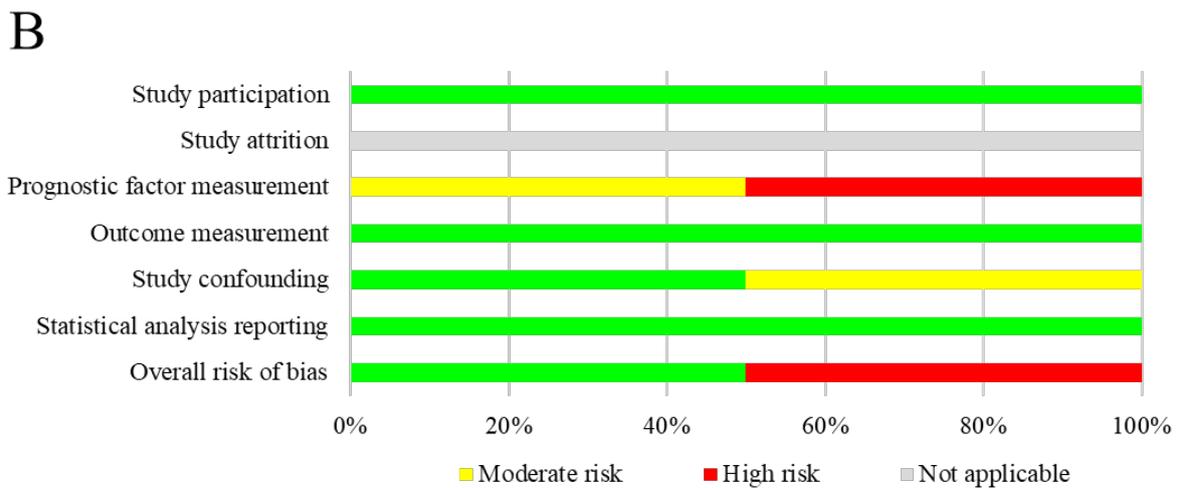
For details, please see the protocol for risk of bias assessment above.

Figure S6 — Length of hospital stay

**A**

n.a. Not applicable  
 + Low risk  
 ? Moderate risk  
 - High risk

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias	Included in meta-analyses
Blomaard, L. C. et al. (2021)	+	n.a.	-	+	?	+	-	Yes
Osuafor C.N. et al. (2021)	+	n.a.	?	+	+	+	+	Yes

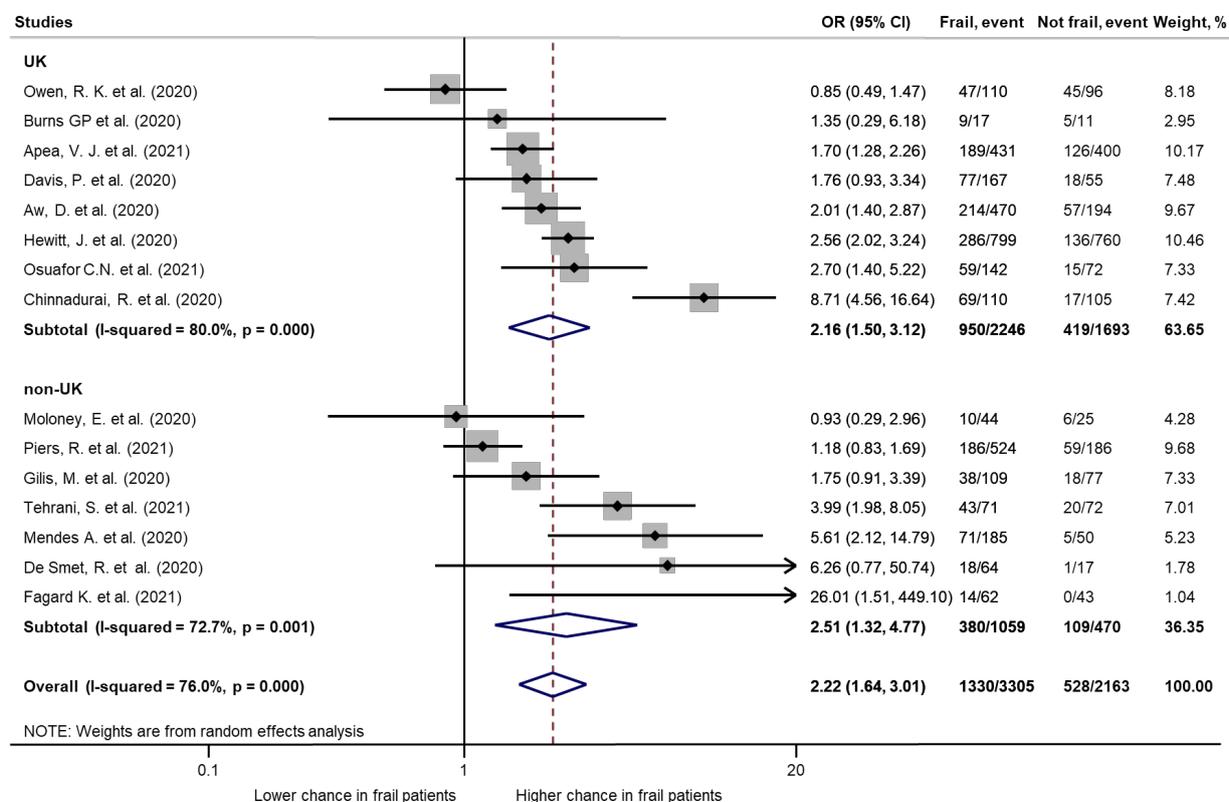


**Figure S6 Risk of bias assessment on study level [A] and across studies [B] reporting length of stay in frail versus not frail patients**

For details, please see the protocol for risk of bias assessment above.

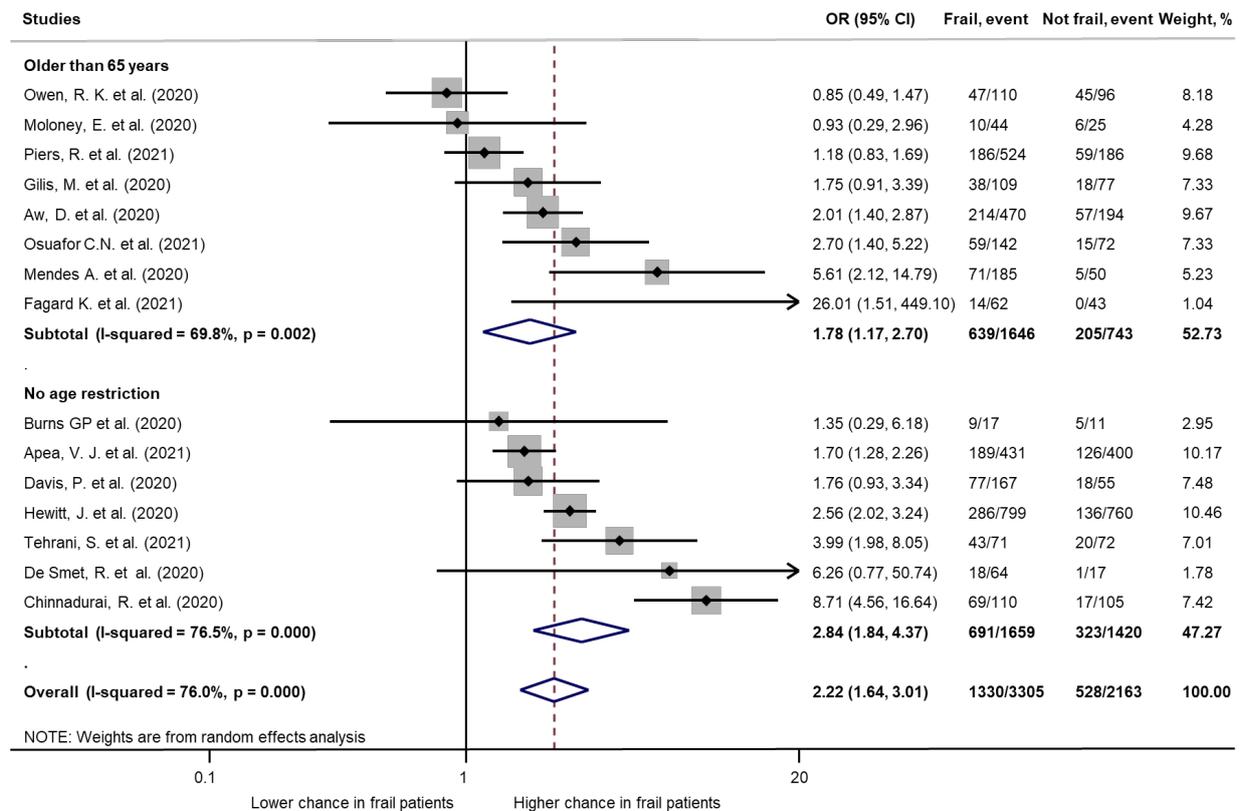
## CFS 1–4 vs 5–9

Figure S7 — Forest plot grouped by country



**Figure S7 Mortality in frail patients indicated by CFS (1–4 vs 5–9), with studies grouped by country** Studies from the UK have an overall odds ratio of 2.16 (CI: 1.50–3.12) for mortality in frail patients (CFS 5–9) while studies outside the UK (non-UK) showed a similar subtotal OR of 2.51 (CI: 1.64–3.01). Note that heterogeneity was significant in both subgroups and for the overall result as well. OR: odds ratio; CI: confidence interval. P<0.1 was considered significant.

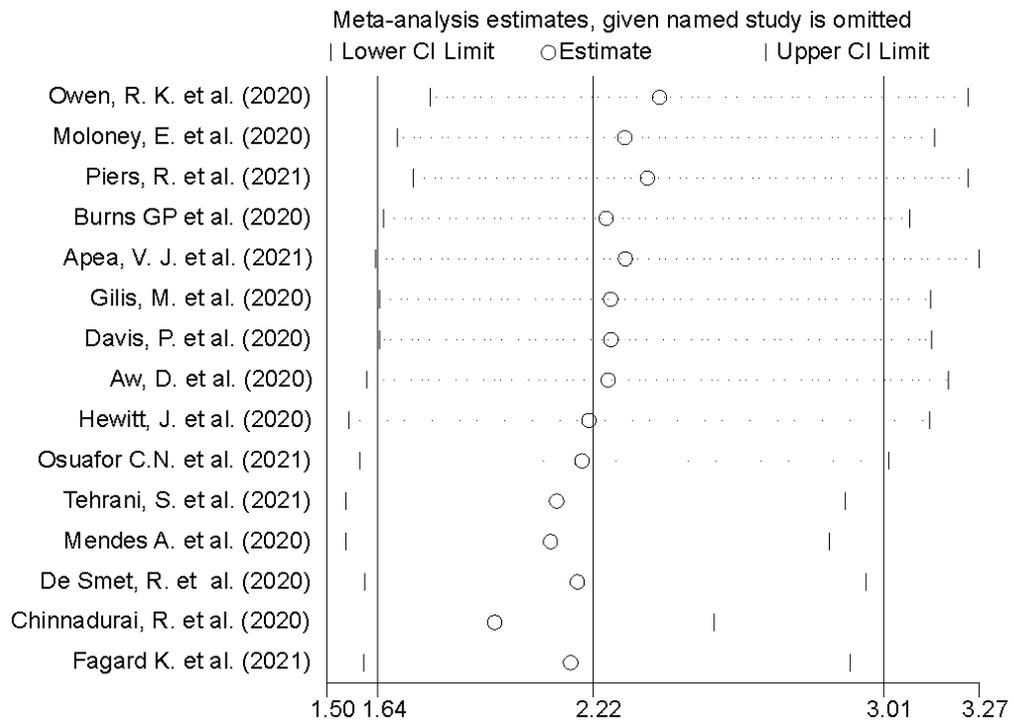
Figure S8 — Forest plot grouped by age restriction



**Figure S8 Mortality in frail patients indicated by CFS (1–4 vs 5–9), with studies grouped by age restriction**

Studies only enrolling patients older than 65 years of age have an overall odds ratio of 1.78 (CI: 1.17–2.70) for mortality in frail patients (CFS 5–9) while studies without age restriction have an overall OR of 2.84 (CI: 1.84–4.37). Note that heterogeneity was significant in both subgroups and for the overall results as well. OR: odds ratio; CI: confidence interval. P<0.1 was considered significant.

Figure S9 — Leave-one-out analysis

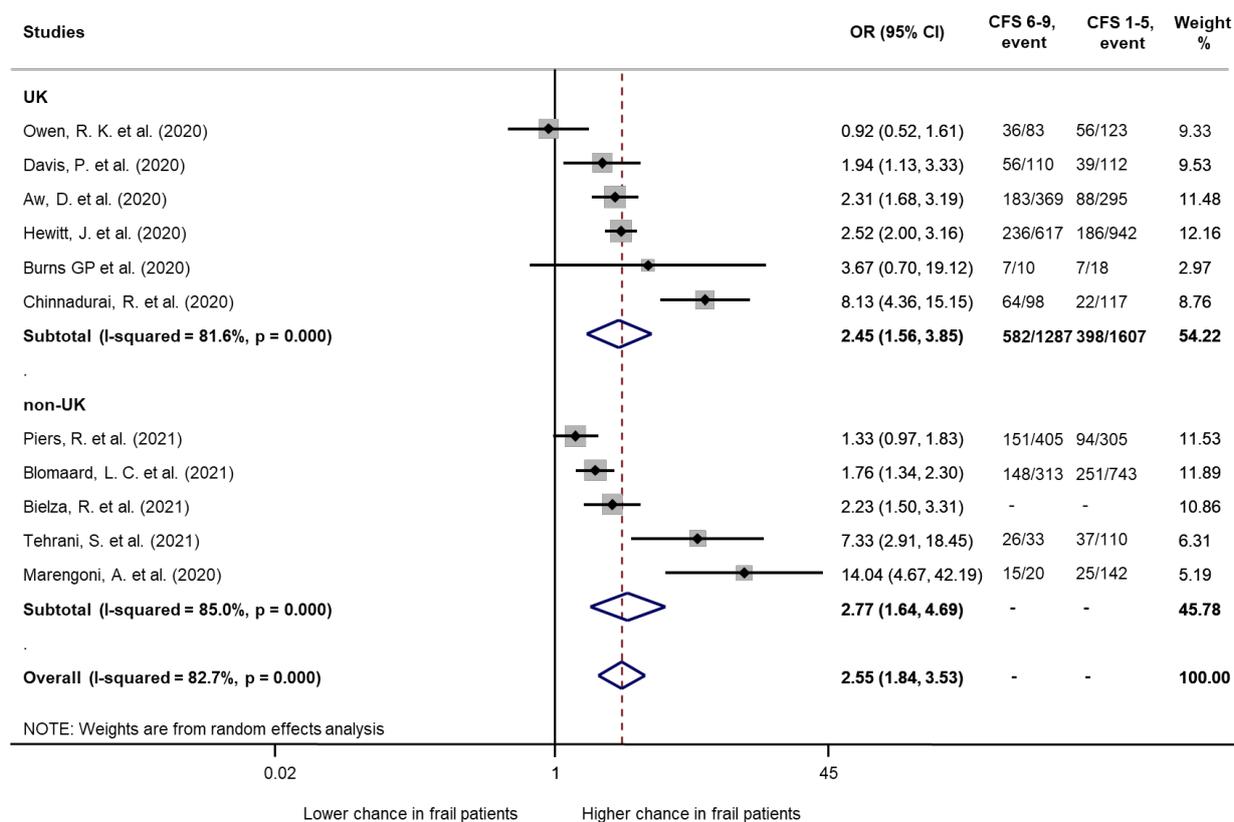


**Figure S9 Leave-one-out sensitivity analysis for studies reporting mortality in patients with CFS 1–4 vs CFS 5–9**

Each row shows the overall OR and CI with the omission of the indicated study. There is no study the omission of which would change statistical significance.

## CFS 1–5 vs 6–9

Figure S10 — Forest plot grouped by country



**Figure S10 Mortality comparing CFS 1–5 and CFS 6–9 groups, with studies grouped by country**

Studies from the UK have an overall odds ratio of 2.45 (CI: 1.56–3.85) for mortality in frail patients (CFS 6–9) while studies outside the UK (non-UK) showed a similar subtotal OR of 2.77 (CI: 1.64–4.69). Note that heterogeneity was significant in both subgroups and for the overall results as well. OR: odds ratio; CI: confidence interval.  $P < 0.1$  was considered significant.

Figure S11 — Forest plot grouped by age restriction

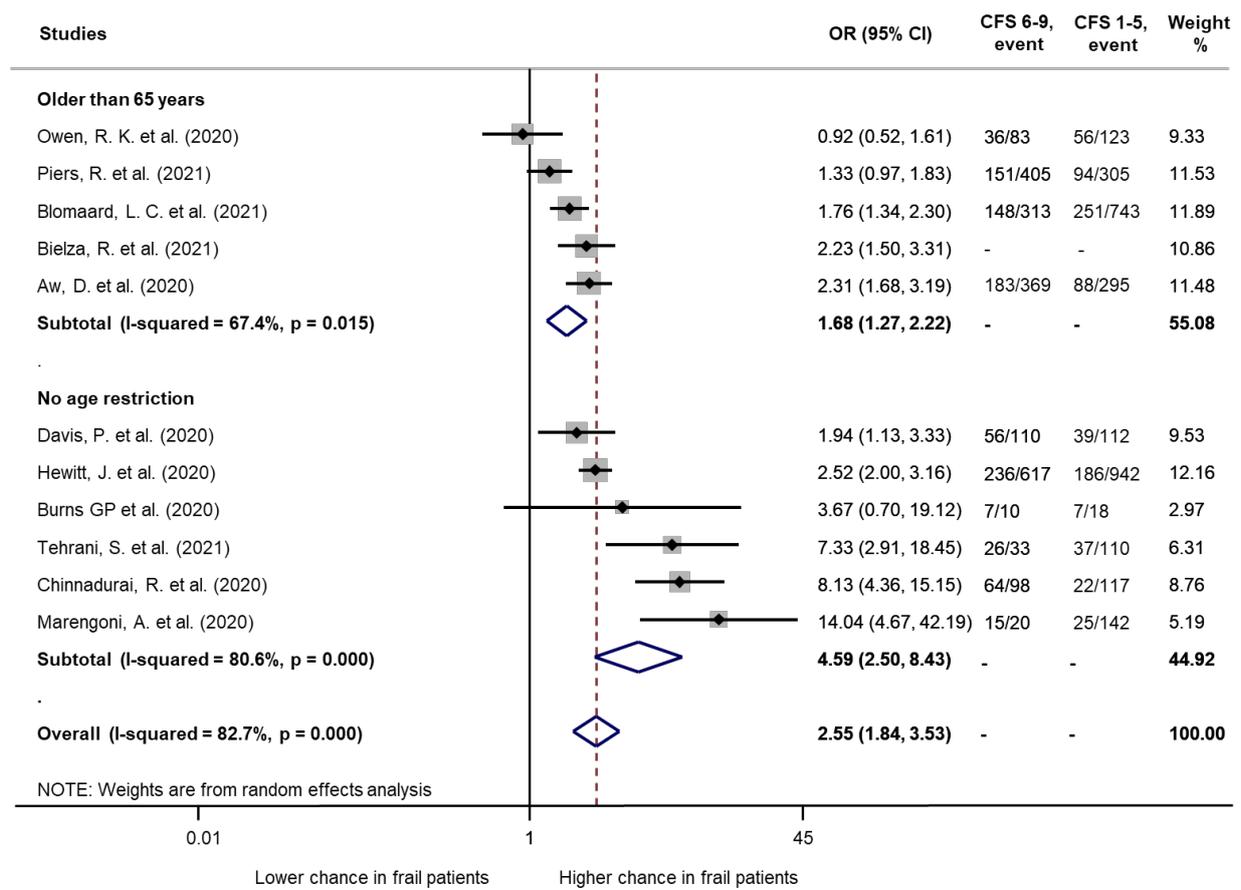
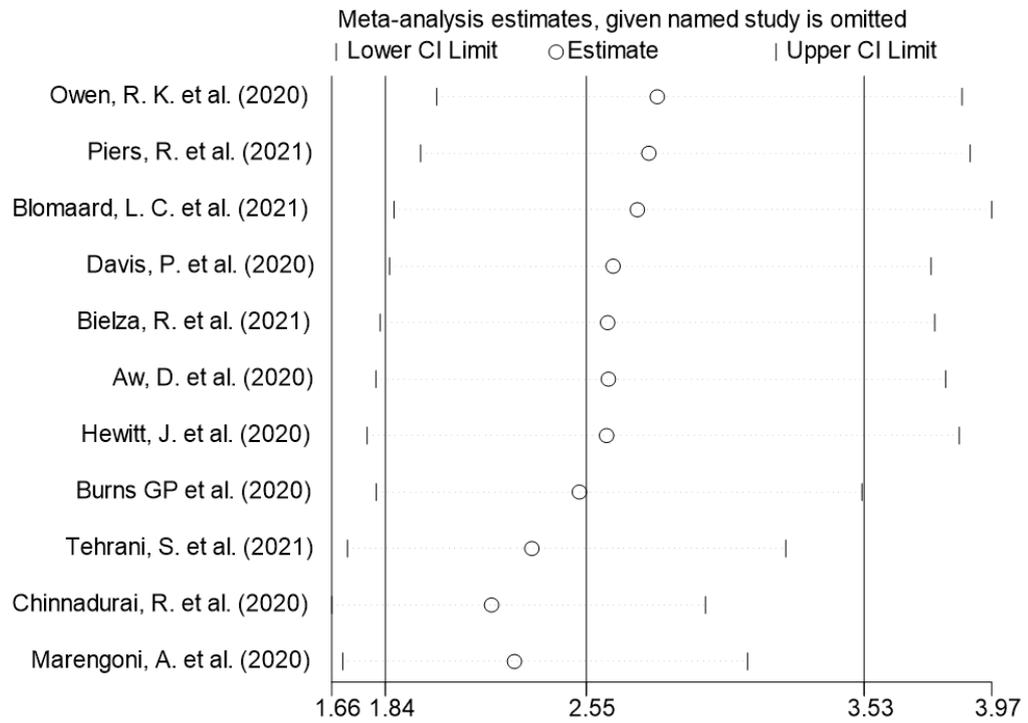


Figure S11 Mortality comparing CFS 1–5 and CFS 6–9 groups, with studies grouped by age restriction

Studies only enrolling patients older than 65 years of age have an overall odds ratio of 1.68 (CI: 1.27–2.22) for mortality in frail patients (CFS 6–9) while studies without age restriction have an overall OR of 4.59 (CI: 2.50–8.43). Note that heterogeneity was significant in both subgroups and for the overall result as well. OR: odds ratio; CI: confidence interval.  $P < 0.1$  was considered significant.

Figure S12 — Leave-one-out analysis



**Figure S12 Leave-one-out sensitivity analysis for studies reporting mortality in patients with CFS 1–5 vs CFS 6–9**

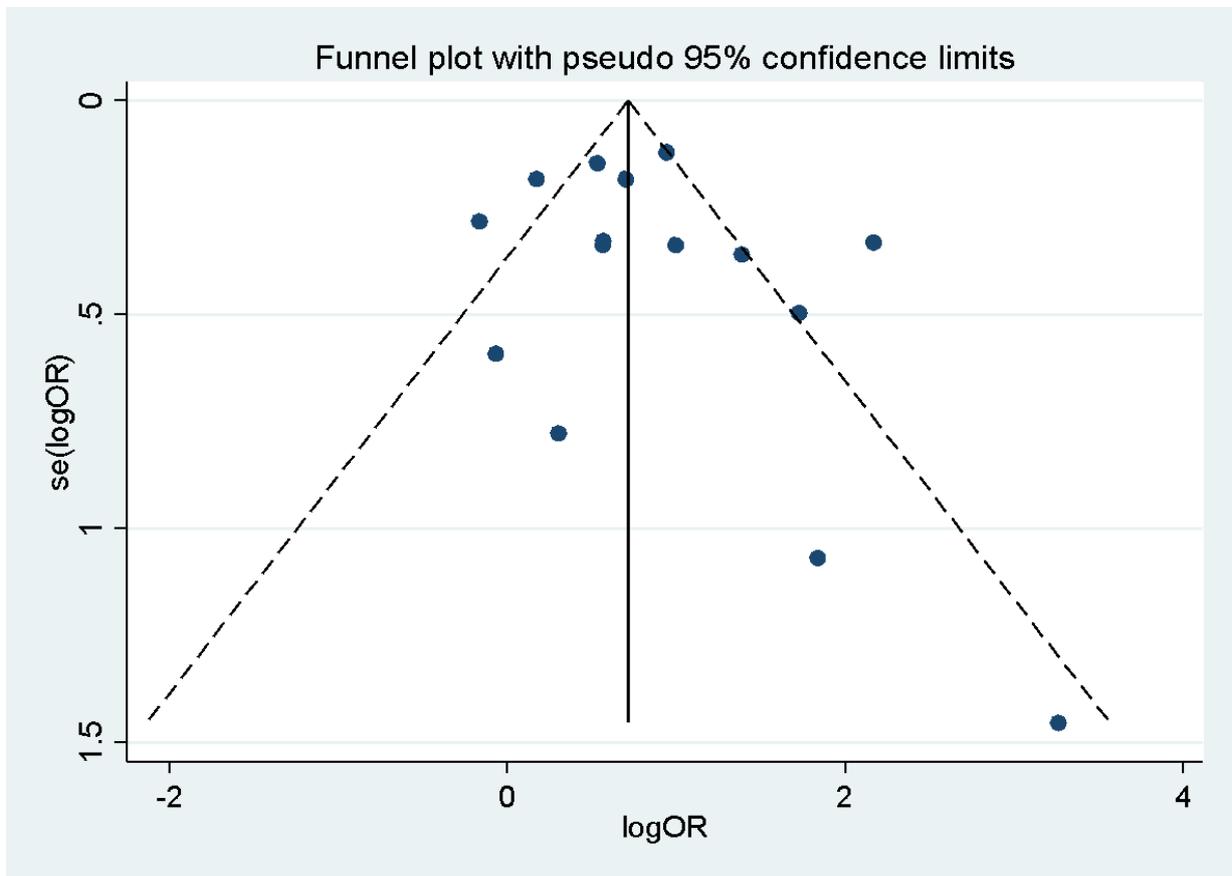
Each row shows the overall OR and CI with the omission of the indicated study. There is no study the omission of which would change statistical significance.





## Funnel Plots

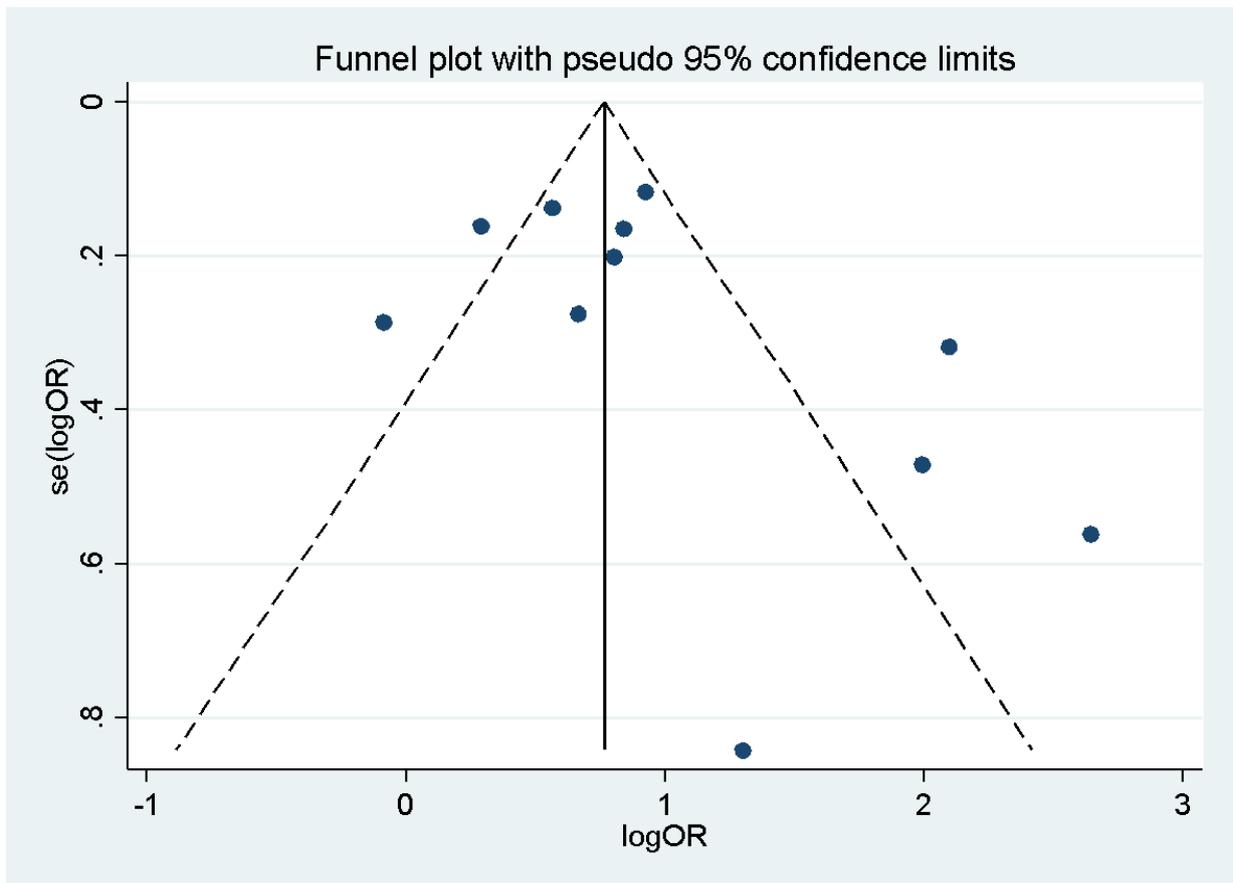
Figure S15 — CFS 1–4 vs 5–9



**Figure S15 Funnel plot for mortality in patients with CFS 5–9 vs CFS 1–4**

Based on the visual inspection of the funnel plot and the result of the Eggers' test ( $p=0.430$ ) no small study effect was identified.

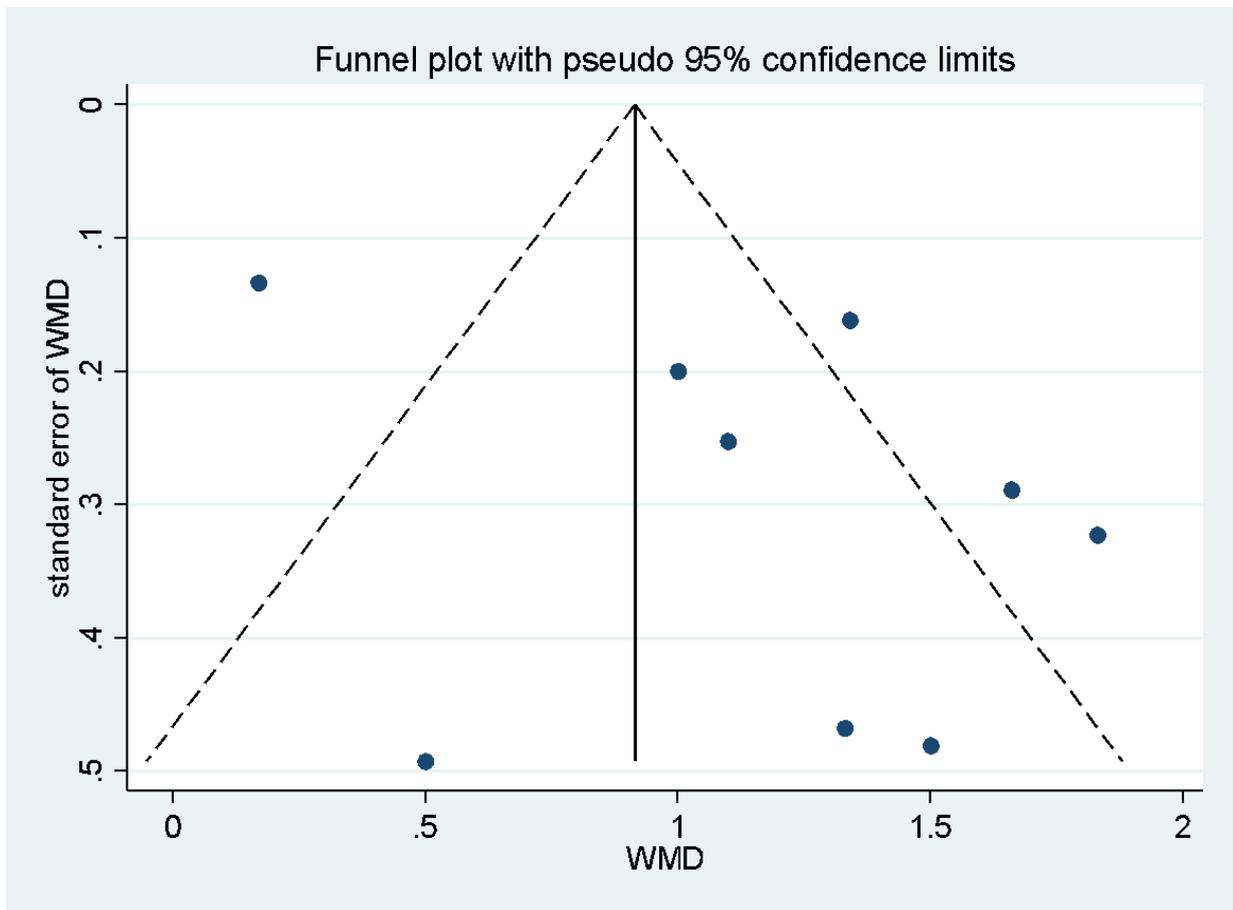
Figure S16 — CFS 1–5 vs 6–9



**Figure S16 Funnel plot for mortality in patients with CFS 6–9 vs CFS 1–5**

Based on the visual inspection of the funnel plot and the result of the Eggers' test ( $p=0.187$ ) no small study effect was identified.

Figure S17 — Weighted Mean Difference



**Figure S17 Funnel plot for frailty difference in survivors vs non-survivors**

Based on the visual inspection of the funnel plot no small study effect was identified. Eggers' test was not conducted due to the low number of studies.

## References

1. Hayden JA, Côté P, Bombardier C: **Evaluation of the Quality of Prognosis Studies in Systematic Reviews**. *Annals of Internal Medicine* 2006, **144**(6):427-437.
2. Grooten WJA, Tseli E, Äng BO, Boersma K, Stålnacke B-M, Gerdle B, Enthoven P: **Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS—aspects of interrater agreement**. *Diagnostic and Prognostic Research* 2019, **3**(1):5.