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Review Article

Factors associated with mortality in patients with COVID-19 admitted to intensive care: a systematic review and meta-analysis

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Summary

Identification of high-risk patients admitted to intensive care with COVID-19 may inform management strategies. The objective of this meta-analysis was to determine factors associated with mortality among adults with COVID-19 admitted to intensive care by searching databases for studies published between 1 January 2020 and 6 December 2020. Observational studies of COVID-19 adults admitted to critical care were included. Studies of mixed cohorts and intensive care cohorts restricted to a specific patient sub-group were excluded. Dichotomous variables were reported with pooled OR and 95%CI, and continuous variables with pooled standardised mean difference (SMD) and 95%CI. Fifty-eight studies (44,305 patients) were included in the review. Increasing age (SMD 0.65, 95%CI 0.53–0.77); smoking (OR 1.40, 95%CI 1.03–1.90); hypertension (OR 1.54, 95%CI 1.29–1.85); diabetes (OR 1.41, 95%CI 1.22–1.63); cardiovascular disease (OR 1.91, 95%CI 1.52–2.38); respiratory disease (OR 1.75, 95%CI 1.33–2.31); renal disease (OR 2.39, 95%CI 1.68–3.40); and malignancy (OR 1.81, 95%CI 1.30–2.52) were associated with mortality. A higher sequential organ failure assessment score (SMD 0.86, 95%CI 0.63–1.10) and acute physiology and chronic health evaluation-2 score (SMD 0.89, 95%CI 0.65–1.13); a lower PaO_2:F_IO_2 (SMD −0.44, 95%CI −0.62 to −0.26) and the need for mechanical ventilation at admission (OR 2.53, 95%CI 1.90–3.37) were associated with mortality. Higher white cell counts (SMD 0.37, 95%CI 0.22–0.51); neutrophils (SMD 0.42, 95%CI 0.19–0.64); D-dimers (SMD 0.56, 95%CI 0.43–0.69); ferritin (SMD 0.32, 95%CI 0.19–0.45); lower platelet (SMD −0.22, 95%CI −0.35 to −0.10); and lymphocyte counts (SMD −0.37, 95%CI −0.54 to −0.19) were all associated with mortality. In conclusion, increasing age, pre-existing comorbidities, severity of illness based on validated scoring systems, and the host response to the disease were associated with mortality; while male sex and increasing BMI were not. These factors have prognostic relevance for patients admitted to intensive care with COVID-19.

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Introduction

COVID-19 requiring admission to ICU has been associated with a high mortality [1], with data reporting a mortality of 41.6% [1]. A more recent meta-analysis which included the African COVID-19 Critical Care Outcomes Study reported ICU mortality of 31.5% [2]. Despite the poor outcomes, the current clinical problem remains that the factors associated with ICU mortality are poorly described [3]. Understanding the factors associated with mortality may allow for appropriate risk stratification and management of these critically ill patients.

With the large volume of peer-reviewed publications relating to COVID-19 patient outcomes, it may be possible to describe the factors associated with mortality among patients admitted to ICU. Currently, we are only aware of systematic reviews which have described factors associated with mortality with unselected cohorts of COVID-19 patients [4], and not critically ill patients with COVID-19. The objective of this systematic review and meta-analysis of observational studies was to determine which factors are associated with mortality in adult patients with COVID-19 admitted to ICU.

Methods

This study is reported in accordance with the PRISMA statement [5]. We included all observational studies (prospective and retrospective) of adult patients with COVID-19 admitted to ICU, reporting mortality or survival outcomes stratified by patient factors, risk scores and haematological results of interest. We excluded studies with mixed cohorts (i.e. not limited to patients admitted to ICU); ICU cohorts restricted to a specific patient sub-group; studies investigating drug efficacy; and review articles.

Studies were identified through a comprehensive and systematic search of the following databases: MEDLINE, Embase, the Cochrane Library, Africa-Wide Information via EBSCOhost and SciELO Citation Index via Web of Science. Databases were searched from 1 January 2020 to 10 November 2020, with an updated search on 6 December 2020. The search encompassed terms relating to COVID-19 and intensive care. This search was supplemented by a manual search up to 21 February 2021. The full search strategy can be found in the online Supporting Information (Appendix S1).

Results from each database were imported to Mendeley reference management software (Elsevier, Amsterdam, Netherlands) and duplicates removed. Titles and abstracts were screened for eligibility by two authors independently based on predefined criteria. The full texts of articles possibly eligible for inclusion were reviewed independently by two authors. Discrepancies were resolved by a third reviewer (ET or BB). Two reviewers independently extracted data from eligible texts (and relevant supplementary material) using a standardised piloted form. Discrepancies were resolved by mutual agreement or by a third reviewer (ET or BB). The reference lists of other reviews were screened for further eligible texts.

We extracted the following information for each study: study design (prospective or retrospective); study location; and the length and location of follow up. For dichotomous variables we collected data on the number of patients who died and survived, stratified by: patient factors (sex; smoking; hypertension; cardiovascular disease; pre-existing respiratory disease; renal disease; diabetes; malignancy; cerebrovascular disease; liver disease); and respiratory support (invasive mechanical ventilation on ICU admission). The original study definitions for the presence of comorbidities were adopted for this review. For continuous variables, we collected summary data (mean and SD or median and IQR) for the overall cohort, survivors and those who died for: patient factors (age; BMI); intensive care risk stratification scores (sequential organ failure assessment (SOFA) score; acute physiology and chronic health evaluation-2 (APACHE-2) score; respiratory support (PaO_2:F_IO_2 ratio on admission to ICU); and haematological factors (D-dimer; ferritin; platelets; haemoglobin; white blood cells; neutrophils; lymphocytes).

We used a modified Newcastle-Ottawa Scale to assess the methodological quality of each included study [6], and this is shown in the online Supporting Information (Appendix S2). Studies scoring 7–9 points were considered high quality, with studies scoring ≤ 6 considered low quality. Modified Newcastle-Ottawa Scale assessments were conducted independently by two reviewers.

We summarised cohort characteristics for dichotomous variables by calculating the proportion of those with each factor in the overall cohort, survived and died groups; for continuous variables, we calculated the pooled estimate

mean and 95%CI for the overall cohort, survived and died groups. To assess the association of the factors of interest with mortality we calculated the pooled OR and 95%CI for dichotomous variables and the pooled standardised mean difference (SMD) and 95%CI for continuous variables. Data reported as median and IQR or range were converted to mean and SD using the formula described by Wan et al. [7]. We assessed the τ^2 and I^2 statistics as measures of statistical inconsistency and heterogeneity, respectively. A random-effects model was adopted if there was moderate (25–50%) or high (> 50%) between-study heterogeneity as assessed by the I^2 test. The random-effects meta-analysis was conducted using the Sidik–Jonkman method. The analysis was conducted using Stata version 16 (StataCorp. 2019, College Station, TX, USA). Funnel plots were generated to assess publication bias. A post-hoc decision was taken to conduct a sensitivity analysis of haematological factors where we excluded studies when it was unclear if the haematological tests were conducted at ICU admission.

Results

Study screening and selection is shown in Fig. 1. In total, 6498 abstracts were screened, with 751 full-text reviews. Fifty-eight studies with 44,305 patients were included in the review [2, 8-65]. These included studies provided data on mortality or survival following ICU admission for 43,845 (99.0%) of the patients.

The included study and patient cohort characteristics are shown in the online Supporting Information (Appendix S3) and the full reference list in the online Supporting Information (Appendix S4). Fifteen (25.9%) of the studies were prospective, and 12 (20.7%) were multicentre studies. The summarised cohort characteristics for each factor of interest are shown in Tables 1 and 2. There were predominantly male patients (68.9%) with a mean (95%CI) age of 61.8 (60.7–63.0) years. The two most common comorbidities were hypertension (47.7%) and diabetes (26.9%). The majority of patients required invasive mechanical ventilation on admission to ICU (54.0%) with a high mean (95%CI) SOFA score of 5.7 (5.1–6.3) and APACHE-2 score of 15.7 (14.7–16.6). The Newcastle-Ottawa Scale risk of bias assessment is shown in the online Supporting Information (Appendix S5). Overall, 45/58 (77.6%) studies were deemed to be high quality.

There was moderate or high heterogeneity across all analyses, and therefore all analyses were conducted with random-effects models. Increasing age (SMD 0.65, 95%CI 0.53–0.77); smoking (OR 1.40, 95%CI 1.03–1.90); hypertension (OR 1.54, 95%CI 1.29–1.85); diabetes (OR 1.41, 95%CI 1.22–1.63); cardiovascular disease (OR 1.91, 95%CI 1.52–2.38); respiratory disease (OR 1.75, 95%CI 1.33–2.31); renal disease (OR 2.39, 95%CI 1.68–3.40); and malignancy (OR 1.81, 95%CI 1.30–2.52) were associated with mortality following ICU admission. A higher SOFA score (SMD 0.86, 95%CI 0.63–1.10) and APACHE-2 score (SMD 0.89, 95%CI 0.65–1.13); a lower PaO_2:F_IO_2 (SMD −0.44, 95%CI −0.62 to −0.26) and the need for mechanical ventilation at admission (OR 2.53, 95%CI 1.90–3.37) were all associated with mortality. Higher white cell counts (SMD 0.37, 95%CI 0.22–0.51); neutrophils (SMD 0.42, 95%CI 0.19–0.64); D-dimers (SMD 0.56, 95%CI 0.43–0.69); ferritin (SMD 0.32, 95%CI 0.19–0.45); lower platelet counts (SMD −0.22, 95%CI −0.35 to −0.10); and lymphocyte counts (SMD −0.37, 95%CI −0.54 to −0.19), were all associated with mortality. Sex, BMI, cerebrovascular disease, liver disease and admission haemoglobin concentration were not associated with mortality following ICU admission (Figs. 2 and 3; see also online Supporting Information, Figures S1–S23).

Funnel plots are shown in the online Supporting Information (Figures S24–S46). These show asymmetry for BMI, cerebrovascular disease and serum ferritin. All other plots appear symmetrical. Sensitivity analyses are shown in the online Supporting Information (Figures S47–S53). Sensitivity analyses included only haematological tests where it was clear that these were taken at the time of admission to ICU. The findings of the sensitivity analysis did not differ from the main findings, except for the neutrophil count which crossed the line of no effect (SMD 0.29, 95%CI −0.05 to 0.62).

Discussion

The principal findings of this meta-analysis are that increasing age; smoking; hypertension; diabetes; cardiovascular disease; respiratory disease; renal disease; and malignancy were associated with ICU mortality in patients with COVID-19. At admission to ICU, higher SOFA and APACHE-2 scores, a lower PaO_2:F_IO_2 and the need for invasive mechanical ventilation were all associated with mortality. Higher white cell counts; neutrophils; D-dimers; ferritin; lower platelet; and lymphocyte counts were also associated with mortality.

The findings confirm the association between diabetes, cardiovascular and respiratory comorbidities with mortality in COVID-19 patients. However, the reported associations between male sex and increasing BMI are not supported by this meta-analysis [66]. This meta-analysis provides a large sample size with respect to these risk-factors and is a robust estimate of risk associated with male sex and BMI. The

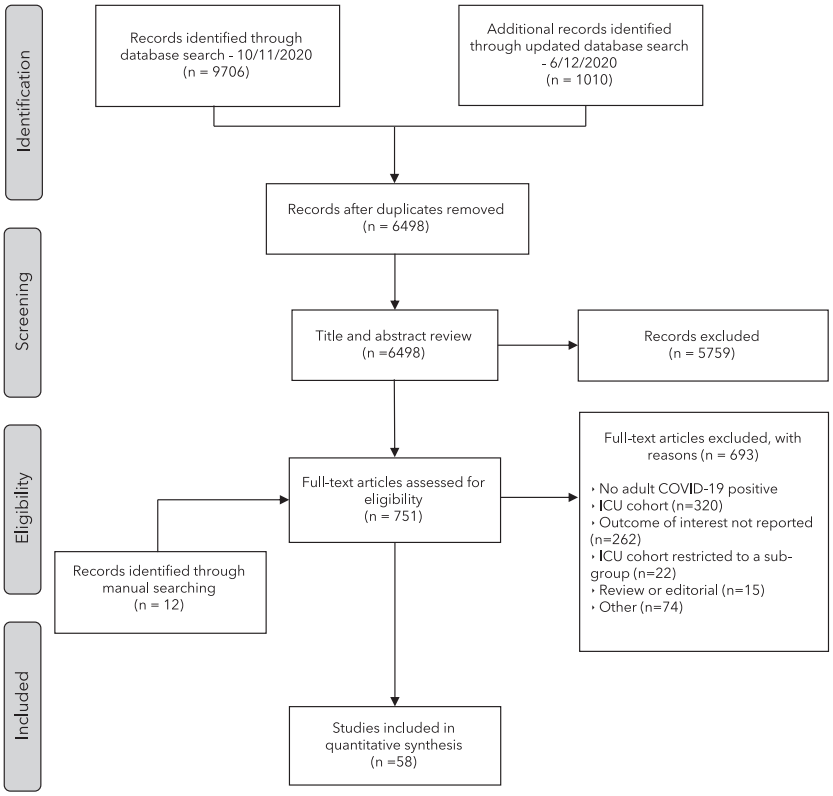

Figure 1 Flow diagram of study screening and inclusion.

previously described obesity paradox in which patients admitted to ICU with higher BMI have more favourable outcomes [67] is not supported by our findings. The previously described association between male sex and mortality [68-70] may need to be questioned further in light of these findings, particularly in the context of those admitted to ICU.

The associations with ICU mortality demonstrated in this meta-analysis may provide direction for future COVID-19-specific prognostic research. Age may be a surrogate for frailty in patients with COVID-19 [71]. The risk-factors of hypertension, smoking and respiratory disease may all be partially related to increased risk associated with angiotensin-converting enzyme (ACE) receptors, as seen by the increased expression of ACE-2 receptors among smokers and patients with chronic obstructive pulmonary disease [72, 73]. The association between hypertension and cardiovascular disease, and increased mortality may potentially increase the risk of cardiac injury associated with the systemic inflammatory response to COVID-19 infection [74, 75].

The inflammatory response associated with mortality appears to be dysregulated in response to COVID-19, and it is likely to drive the high mortality in critically ill patients with COVID-19 [76]. Previously, a smaller meta-analysis has shown that a higher neutrophil:lymphocyte ratio is associated with mortality [77]. Our meta-analysis supports this finding with a significantly higher neutrophil count and significantly lower lymphocyte count associated with mortality. Furthermore, the inflammatory effects of a high ferritin, high D-dimers and low platelet counts could both precipitate or be the result of thrombotic and coagulopathic effects [78]. Our meta-analysis suggests that there is little difference between the SOFA or APACHE-2 risk stratification scores at critical care admission in patients with COVID-19, although other studies have suggested that the APACHE-2 score may be better at predicting mortality among severely ill patients with COVID-19 than the SOFA score [64]. Simpler scores, such as the quick SOFA may not have equivalent prognostic performance to the SOFA or APACHE-2 scores [79], but may have clinical utility in lower resource environments where access to a full blood profile is not universally available [2].

One limitation of this meta-analysis is that it does not allow us to risk-adjust between risk factors associated with ICU mortality. Risk adjustment is important in accurate prognostication for ICU admission. Some of the included studies have provided risk-adjusted (multivariable adjusted) risk-factors. Of the prospective observational studies, the largest studies which provide data are the Intensive Care

Table 1 Characteristics of the dichotomous variable risk-factors reported in patients with COVID-19 admitted to ICU. Numbers are value, or value (proportion).

	Studies	Patients	Total with characteristic	With characteristic survived/total survived	With characteristic died/total died
Sex; male	55	43,355	29,889 (68.9%)	17,587/26,144 (67.3%)	12,302/17,211 (71.5%)
Renal disease	28	13,926	952 (6.8%)	420/7997 (5.3%)	532/5929 (9.0%)
Cardiovascular disease	41	16,205	2097 (12.9%)	978/9378 (10.4%)	1119/6827 (16.4%)
Hypertension	45	20,496	9767 (47.7%)	5374/12,240 (43.9%)	4393/8256 (53.2%)
Respiratory disease	41	16,353	1056 (6.5%)	514/9406 (5.5%)	542/6947 (7.8%)
Diabetes	47	20,910	5627 (26.9%)	3029/12,530 (24.2%)	2598/8380 (31.0%)
Malignancy	29	14,272	801 (5.6%)	356/8102 (4.4%)	445/6170 (7.2%)
Smoking	21	12,627	1579 (12.5%)	931/7801 (11.9%)	648/4826 (13.4%)
Liver disease	17	9674	223 (2.3%)	109/5128 (2.1%)	114/4546 (2.5%)
Cerebrovascular disease	12	5013	266 (5.3%)	124/2639 (4.7%)	142/2374 (6.0%)
Mechanical ventilation on admission	6	14,504	7826 (54.0%)	4234/8546 (49.5%)	3592/5958 (60.3%)

Table 2 Characteristics of the continuous variable risk-factors reported in patients with COVID-19 admitted to ICU. Numbers are value or pooled mean (95%CI).

	Studies	Patients	Overall pooled estimate	Survived pooled estimate	Died pooled estimate
Age; y	51	27,149	61.8 (60.7-63.0)	58.4 (57.1-59.6)	66.8 (65.4-68.1)
BMI; $kg.m^{-2}$	21	21,243	28.9 (28.2-29.7)	28.7 (27.9-29.5)	29.0 (28.3-29.7)
SOFA	24	8650	5.7 (5.1-6.3)	4.7 (4.0-5.4)	7.0 (6.4-7.7)
APACHE-2	21	13,456	15.7 (14.7-16.6)	13.4 (12.3-14.5)	18.3 (17.2-19.4)
PaO_2:F_IO_2 ratio	20	17,825	126.4 (117.2-135.6)	137.9 (126.6-149.1)	109.5 (98.1-121.0)
D-dimer	32	9239	*	*	*
Neutrophils	14	2678	*	*	*
White blood Cells	31	8075	*	*	*
Ferritin	13	2345	*	*	*
Haemoglobin	17	4392	*	*	*
Lymphocytes	29	11,083	*	*	*
Platelets	27	9131	*	*	*

SOFA, sequential organ failure assessment; APACHE-2, acute physiology and chronic health evaluation 2.
*Pooled mean (95%CI) for haematological results were not estimated due to different units used to report these tests. Summary estimates of risk for mortality associated with haematological results (shown in Fig. 3) were calculated using standardised mean difference, which accounts for variation in reported units.

National Audit and Research Centre (ICNARC) [25, 65], the COVID-ICU Group study from Europe [18] and the African COVID-19 Critical Care Outcomes Study (ACCCOS) [2]. These large prospective observational studies have confirmed an independent association with increasing age, immunosuppression, diabetes, cardiovascular and renal disease, ICU severity scores and a lower PaO_2:F_IO_2 ratio with mortality [2, 18, 19]. While increasing respiratory and ventilatory support at admission were also associated with mortality in this meta-analysis, these findings should be viewed with caution. They may reflect resource and management factors or deterioration before critical care admission, which may bias the estimates of risk. Without more nuanced data on the effect of resource availability and management strategies before admission, it is impossible to determine the association between the PaO_2:F_IO_2 ratio and the need for invasive mechanical ventilation at admission on outcome. It is likely that the prognostic

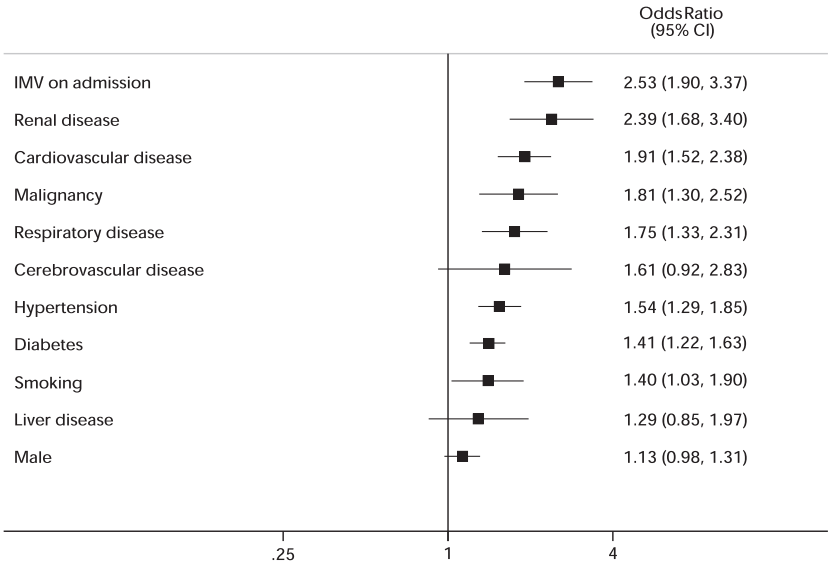

Figure 2 Summary estimates of risk for mortality following critical care admission associated with dichotomous variables (patient characteristics; comorbidities; and invasive mechanical ventilation (IMV) on admission).

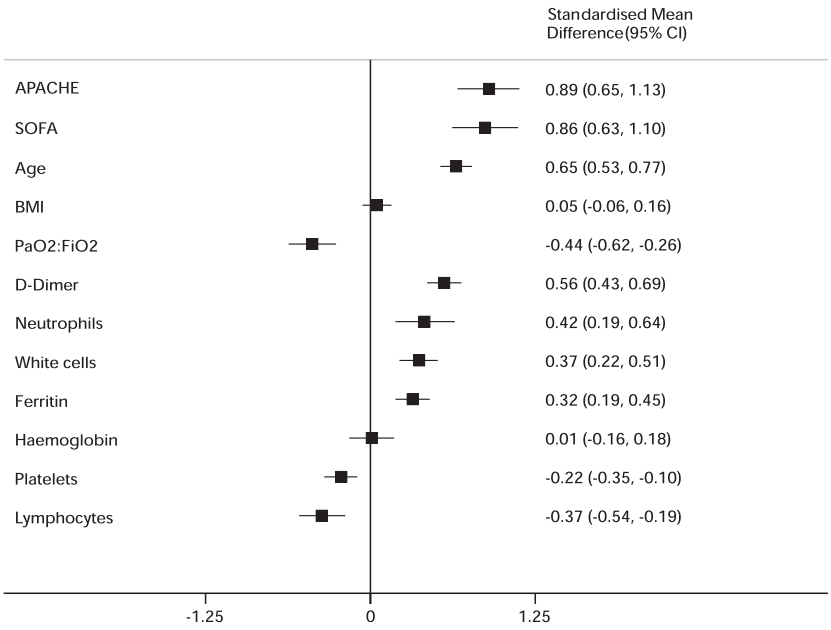

Figure 3 Summary estimates of risk for mortality following critical care admission associated with continuous variables (patient factors; risk scores; and haematological results at admission). SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation-2.

importance of these risk-factors will be difficult to determine, especially as a recent meta-analysis of early vs. late tracheal intubation in patients with COVID-19 requiring mechanical ventilation did not show a difference in outcome between the two strategies [80].

This meta-analysis did not assess some factors that may be prognostically important in critically ill patients with COVID-19, such as a short duration of time between first symptoms and ICU admission [18] and HIV/AIDS [2]. Furthermore, the association between C-reactive protein,

interleukin-6 or procalcitonin and mortality were also not evaluated [81]. The impact of therapies such as dexamethasone and tocilizumab were not examined in this meta-analysis [82, 83].

Finally, this meta-analysis is characterised by high heterogeneity despite using random-effects models. This may be partly due to the different definitions used for the risk-factors across the included studies.

In conclusion, increasing age, pre-existing comorbidities and greater severity of illness are associated with mortality in patients admitted to ICU with COVID-19, but male sex and increasing BMI were not. The host response to disease as manifested by various inflammatory and thrombotic markers and the severity of respiratory failure also predicts outcome. Requiring invasive mechanical ventilation on admission to ICU was a significant predictor of mortality although resources, management strategies and pre-admission deterioration may all modify this risk-factor.

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Supporting Information

Additional supporting information may be found online via the journal website.

Figure S1–S23. Forest plots demonstrating associations between characteristics and mortality in COVID-19 patients admitted to critical care.

Figure S24–S46. Funnel plots of studies reporting the associations between characteristics and mortality in COVID-19 patients admitted to critical care.

Figure S47–S53. Sensitivity analyses with forest plots demonstrating associations between characteristics and mortality in COVID-19 patients admitted to critical care.

Appendix S1. Search strategy used for this systematic review.

Appendix S2. Modified Newcastle-Ottawa Quality Assessment Scale.

Appendix S3. Study and cohort characteristics of studies included in the review.

Appendix S4. Reference list of studies included in the review.

Appendix S5. Methodological quality assessment of included studies.

Appendix S6. PRISMA checklist.