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Review Article

Hospital readmission after critical care survival: A systematic review and meta-analysis

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Summary

Survivors of critical illness frequently require increased healthcare resources after hospital discharge. We undertook a systematic review and meta-analysis to assess hospital readmission rates following critical care admission and to explore potential readmission risk factors. We searched the MEDLINE, Embase and CINAHL databases on 5 March 2020. Our search strategy incorporated controlled vocabulary and text words for hospital readmission and critical illness, limited to English language. Two reviewers independently applied pre-defined eligibility criteria and assessed quality using the Newcastle-Ottawa Score checklist and extracted data. Primary outcome was acute hospital readmission in the year after critical care discharge. Of the 8851 studies screened, 87 met inclusion criteria and 41 were used within the meta-analysis. The analysis incorporated data from 3,897,597 individual patients and 741,664 readmission episodes. Pooled estimates for hospital readmission after critical illness were 16.9% (95% CI: 13.3–21.2) at 30 days; 31.0% (95% CI: 24.3–38.6) at 90 days; 29.6% (95% CI: 24.5–35.2) at six months; and 53.3% (95% CI: 44.4–62.0) at 12 months. Significant heterogeneity was observed across included studies. Three key risk factors contributed to excess acute care rehospitalisation one year after discharge: the presence of comorbidities; events during initial hospitalisation (for example, the presence of delirium and duration of mechanical ventilation); and subsequent infection during the post hospital discharge period. Hospital readmission is common in survivors of critical illness. Careful attention to the management of pre-existing comorbidities during transitions of care may help reduce healthcare utilisation after critical care discharge. Future research should determine if targeted interventions for at-risk critical care survivors can reduce the risk of subsequent rehospitalisation.

Introduction

Survivorship after critical illness brings challenges to patients and their primary caregivers in the months after hospital discharge [1, 2]. These include physical, social, emotional and cognitive problems [3–6]. Critical care survivors frequently require access to outpatient and acute inpatient hospital resources in the post discharge period [7, 8]. Hospital readmission may cause distress for individual patients and their caregivers; and increase strain on the healthcare system [9, 10]. For patients who survive critical care, it is not currently clear what proportion of hospital readmissions are potentially preventable nor the proportion that indicate terminal decline, as observed in other subgroups of the population (e.g. older adults) [11].

A greater understanding of the use of healthcare resources across the clinical recovery continuum, as well as delineation of potential modifiable risk factors, may help support the individual patient as well as the healthcare system. There is therefore a need to synthesise the current evidence base, to inform future interventional work in the field.

We conducted a systematic review and meta-analysis to understand the frequency of hospital readmission after critical care survival. A secondary objective was to evaluate potential risk factors for readmission. We hypothesised there would be a high hospital readmission rate in the months following discharge and that prior health status would play an important contributory role to the use of healthcare resources.

Methods

No ethical approvals were sought for this secondary analysis of previously published data. This systematic review was prospectively registered and conducted and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [12]. The search strategy was formulated according to the CoCoPop (condition, context and population) mnemonic which is recommended for systematic reviews designed to address prevalence and incidence data (Table 1) [13].

Eligible studies had a randomised controlled trial, cohort or case control design. Only studies in which > 50% of the study population had been admitted to a critical care environment were included. Narrative reviews, editorials, case reports, duplicate publications, qualitative studies and conference abstracts were excluded. We also excluded studies that were limited to children or neonates and those that reported readmission to a critical care environment during the same hospital encounter. In addition, we excluded specialist ICU populations (for example, cardiothoracic and neurosurgical) from inclusion in the meta-analysis as the focus was the general critical care population only. Data

on the type of critical care population, including readmission rates and risk factors for hospital readmission, are detailed in online Supporting Information Table S1.

Search Strategy and Sources

Our PROPSERO and Cochrane Library search confirmed that no systematic reviews of hospital readmission after critical illness survival had previously been conducted nor were in progress. We electronically searched MEDLINE and In-Process and Other Non-Indexed Citations 1946 to 4 March 2020 and Embase 1947–present, updated daily, both via OvidSP, and CINAHL 1981 to date via EBSCOhost. As per Cochrane recommendations, no date limit was imposed on the search [14]. Each database was searched individually on 5 March 2020 and not restricted by publication date. We limited our search to human studies and studies published in English. The search strategy, led by an experienced librarian (PC) and reviewed by JM, utilised appropriate subject headings and text words relating to hospital readmission, critical illness and survival (online Supporting Information Appendix S1). We did not update the search before the final analysis as we did not wish to include COVID-19 critical care patients due to the uncertainty about clinical course in this patient cohort (see limitations section).

Study selection

We included studies that met the following criteria: adults (aged > 18 y); inclusion of hospital readmission data; and studies where more than 50% of the population being studied had been admitted to a critical care environment. Each study was independently reviewed for eligibility by two clinicians, first by title and abstract review followed by full text review. Eligibility disagreements were resolved by a third reviewer. We used the Covidence software package (v2619) to undertake the study selection phase and data extraction. When two or more studies reported data from the same patient cohort, the most relevant article was chosen. Of note, a small number of publications included patients from the same cohort but the studies reported hospital readmissions at different time-points. If a study cohort reported on the same cohort of patients but included different longitudinal readmission data, both studies were included in the analysis.

Data extraction

Readmission rate, within the context of this review was defined as the number of patients readmitted to hospital after initial discharge at least once during the study follow-up period. We included the number of patients either alive at the time-point of measurement or, when this was not available, the number of patients discharged alive from hospital. The following information was

extracted from each included article: author; year of publication; country (region); study design; specialist sub-group information; number of sites included (multicentre vs. single centre); patient characteristics (age and sex); readmission rate; number of patients included in the analysis; time-point of measurement; and risk factors for readmission (including patient and hospitalisation characteristics).

Quality assessment

Cohort study quality was assessed using the Newcastle-Ottawa Score checklist [12]. This consists of three main domains to assess quality and risk of bias. These are: patient selection (cohort data source, representativeness and ascertainment of exposure to the outcome of interest); comparability of cohort; and outcome assessment (including adequate follow-up time, acquisition of outcome and adequacy of follow-up). We assessed for risk of bias in the randomised controlled trials in this analysis using the Cochrane risk of bias methodology [14]. Data on risk of bias and overall quality assessment are presented in online Supporting Information Table S2.

Data analysis

Reviewer agreement was assessed with the κ statistic and was interpreted according to Landis and Koch guidelines [15]. Data from eligible studies were pooled for the primary outcomes (hospital readmission). Pooling was undertaken at the four most frequently reported timeframes in the literature: 30 days; 90 days; 6 months and 12 months. Other data were not included in the meta-analysis due to limited data available at these time-points.

We also included a sub-group analysis of studies that examined hospital readmission in patients who had prolonged exposure to critical care, defined as patients ventilated for, or with a critical care stay, of > 7 days. One study also included the definition: "*ventilation for 4 days with a tracheostomy in place, or ventilation for 21 days without a tracheostomy"*. After reviewer discussion, this was included in the prolonged exposure cohort. We limited inclusion to this component of meta-analysis to readmission rates at 12 months after hospital discharge.

Random-effect meta-analysis with Clopper Pearson 95% CIs and 95% prediction intervals (PIs) was used to obtain an estimate of the effect size for the primary outcome measure (hospital readmission). Data were pooled across the entire population and reported from each study. Patients who died in hospital after critical care admission were not included within readmission rate calculations. Random-effects meta-regression log odds were used to estimate pooled proportions of

hospital readmission including; time to readmission (30 days, 90 days, 6 and 12 months); location of study (Europe, Asia, South America, Canada and USA); type of critical care admission (surgical, medical or mixed); and study type (multicentre or single centre). The I^2 statistic was used to assess study heterogeneity. The I^2 represents the percentage of total variance across studies that was attributable to heterogeneity rather than change. Heterogeneity was defined as $I^2 > 50\%$. Analysis was performed using R (V4.10) and data visualisation was undertaken using the R Package ggplot2. All data produced for this analysis are provided in online Supporting Information Table S1. The full R code is included in online Supporting Information Appendix S2.

Results

Article characteristics

Our search strategy identified 9524 records. After duplicates were removed, 8851 were screened for inclusion. Of these, 8540 were excluded based on the title or abstract. Therefore, 87 studies met the eligibility criteria and were included in this analysis (Fig. 1) [16–102]. The κ value for agreement on full text was excellent (0.90, $p < 0.01$). We excluded specialist ICU populations (for example, cardiothoracic and neurosurgical) from inclusion in the meta-analysis as the focus was the general critical care population only. Therefore, 41 studies were included in the meta-analysis.

Summary of studies included

Studies varied widely in their size, methodology, length of follow up and characteristics. Over half of the studies (n = 49, 56.3%) were from the USA, 13 (14.9%) were conducted in Canada, 18 (20.7%) in Europe, 5 (5.7%) in Asia, one (1.2%) in South America and one in Australia (1.2%). Of the 87 studies reported, the majority were observational cohort studies (n = 80, 92%), with four (4.6%) randomised controlled trials and three (3.4%) case control studies. The most frequently used time-point for measuring hospital readmission was 30 days. Twenty-one (23.9%) reported outcomes beyond 12 months. Thirty-nine (44.8%) studies included were single centre and the remaining 48 (55.2%) were multicentre in nature (Table 2). The full characteristics and outcomes of studies included are presented in online Supporting Information Table S1. A summary of the main features of the included studies is presented in Table 2.

Risk of bias

The quality assessment for the included studies is shown in online Supporting Information Table S2. The overall quality of the studies was variable. The median Newcastle-Ottawa score was 6 (IQR 5–7) for the observational/case control studies included. Of the four randomised controlled trials

included, all were deemed to have a high risk of bias in at least four study design domains. Publication bias was visually inspected via random effects funnel plots analysed by timeframe of admission (online Supporting Information Figure S1). These plots suggested that there was heterogeneity of the reported pooled proportions from studies included in the meta-analysis.

Meta-analysis: hospital readmission following critical illness

For the meta-analysis, only hospital readmissions up to 12 months post discharge were included, as these were the most frequently reported outcomes. We did not include studies that reported ICU readmission in isolation or ICU readmission within the same hospital encounter.

Therefore, 41 studies were included in the meta-analysis [17, 19–21, 23, 24, 30, 32, 33, 35, 36, 39, 42–47, 49, 51, 55, 56, 61, 63, 65, 71, 72, 74, 75, 77, 78, 81, 82, 84, 88, 91, 92, 95, 99, 101, 102] (Fig. 2). These represented 3,897,597 patients and 741,664 readmission episodes. Sixteen studies reported outcomes at 30 days, nine at 90 days, eight at 6 months and 14 at 12 months (Fig. 2). Six studies reported readmission rates at multiple time-points. Pooled estimates for hospital readmission after critical illness were 16.9% (95% CI: 13.3–21.2, 95% PI: 5.4–41.8) at 30 days; 31% (95% CI: 24.3–38.6, 95% PI: 11.6–60.7) at 90 days; 29.6% (95% CI: 24.5–35.2, 95% PI: 14.7–50.7) at 6 months; and 53.3% (95% CI: 44.4–62.0, 95% PI: 20.3–83.7) at 12 months. There was evidence of significant heterogeneity across the studies: at 30 days $I^2 = 100\%$ ($p < 0.001$, τ^2 0.3); at 90 days $I^2 = 93\%$ ($p < 0.001$, τ^2 0.2); at 6 months $I^2 = 100\%$ ($p < 0.001$, τ^2 0.1); and 12 months $I^2 = 100\%$ ($p < 0.001$, τ^2 0.4) (Fig. 2).

We conducted sensitivity analyses comprising a random-effects meta-regression examining the following variables: time to readmission (30 days, 90 days, 6 and 12 months); location of study (Europe, Asia, South America, Canada and USA); type of critical care admission (surgical, medical or mixed); and study type (multicentre or single centre). The meta-regression yielded no difference in the heterogeneity reported ($I^2 = 99.9\%$, $p < 0.001$, $\tau^2 = 0.2$) (online Supporting Information Figure S2). We undertook a further sensitivity analysis for those studies deemed to be at very high risk of bias (Newcastle-Ottawa Score ≤ 3 or those deemed to be at high risk of bias using the Cochrane Risk of bias methodology). Again, this yielded no difference in the synthesised results (online Supporting Information Figure S3).

Risk factors for hospital readmission

Utilising study data included in the pooled meta-analysis, 28 studies reported risk factors for readmission. Adverse events during the initial hospitalisation were also cited as risk factors for readmission in 12 (42.9%) of these studies. Risk factors included: comorbid conditions; hospital length of stay; sepsis; delirium; acute kidney injury; and duration of mechanical ventilation during the index hospitalisation. The number of comorbidities (including complex multimorbidity) was cited as a risk factor for readmission in six (21.4%) studies. Two (7.1%) studies identified frailty as a risk factor for hospital readmission. Sepsis during the initial admission or re-infection following discharge was deemed a risk factor for readmission in seven (25%) studies. Details on the individual risk factors identified across all studies included are detailed in online Supporting Information Table S1.

Prolonged critical care exposure

Eight studies explicitly reported the outcomes of prolonged stay or long-term mechanical ventilation patients, defined as patients ventilated for, or with, a critical care stay of > 7 days. In this prolonged critical care exposure cohort, the pooled estimate of hospital readmission was 51.0% at 12 months (95% CI: 0.42–0.59, 95% PI:18.6–82.0) (Fig. 3). There was evidence of heterogeneity across the studies (I^2 = 79%, $p < 0.01$, $\tau^2 = 0.3$). Risk factors for readmission in the prolonged stay cohort were explored in five studies [42, 49, 75, 92, 100] One study reported that prolonged ventilation was a risk factor for readmission at 6 and 12 months post discharge [42], while another reported that those patients with shorter critical care stays were at a higher risk of readmission at 30 days post discharge [75]. Three studies reported that either infection or sepsis were the most common reason for readmission in this sub-group [49, 92, 100].

Discussion

This review has shown that acute rehospitalisation following critical care is common, with up to half of critical care survivors experiencing acute hospital readmission in the year following discharge. Our analysis demonstrates that this population of critical care survivors experience high levels of ongoing needs after their initial illness episode. More work is required to understand how best to support these patients in the post hospital discharge phase.

We identified that multimorbidity before critical illness and baseline frailty were risk factors for hospital readmission. This is consistent with previous qualitative research highlighting the relationship between complex health and psychosocial needs and hospital readmission, especially in the context of multimorbidity and polypharmacy [9]. There are a number of potential clinical interventions that could improve transitions of care for this vulnerable group and potentially reduce

future interactions with acute healthcare. Research has shown that more than half of ICU survivors suffer disruption in their medication regime in the months following discharge [103]. Clinicians should ensure that robust processes are implemented across the recovery journey in relation to medication management [104]. Management of psychosocial, psychological and functional needs for patients, via targeted rehabilitation may also reduce the number of unscheduled healthcare interactions that survivors face. By ensuring that the social environment to which the patients return is supportive and accommodates rehabilitation, there may be less need for hospital readmission [105]. Finally, there is very little evidence available to clinicians about how critical illness may alter the severity or course of long-term conditions such as heart disease and chronic obstructive pulmonary disease. Future research should seek to address this gap, by examining the progression of disease and how best this can be managed.

We also identified that sepsis during the initial hospitalisation or subsequent re-infection after discharge as a risk factor for readmission in 25% of pooled studies. At present, there is limited research that examines longitudinal biological phenotyping across the recovery trajectory for critical care survivors [106]. Thus, it is difficult to establish whether critical care survivors have an ongoing inflammatory process following discharge driving readmission, or whether patients develop new infection. Given the inflammatory nature of most critical illnesses, a working hypothesis could be that there is a deregulated immune response following critical illness. This hypothesis may inform our understanding of therapeutic targets for reducing healthcare utilisation, as well as the global problems experienced by survivors of critical illness. Thoughtful and coherent research is needed in this area to understand any potential biological mechanistic link between this ongoing symptom burden, healthcare utilisation and the complex pathways of inflammation and new or recurrent infection after critical illness.

In this review, we deliberately excluded data from COVID-19 patients as research on their recovery trajectory is still evolving [107]. However, early reports suggest similar rates of readmission have been observed in COVID-19 survivors. For example, in a multicentre study from the USA of over 2000 patients, 27% of COVID-19 hospital survivors were readmitted or died within 60 days of discharge, with COVID-19, sepsis, pneumonia and heart failure the most common reasons for readmission [108]. Moreover, in a national cohort of almost 50,000 COVID-19 survivors in the UK, 29.4% of patients were readmitted after hospital discharge (mean follow-up period 140 days) [109]. Given the often protracted hospital course of COVID-19 patients, it may be that the length and course of

hospitalisation plays a significant role in readmission risk. More work is required to fully delineate this important concept.

This review has demonstrated that those with prolonged critical care exposure had similar rates of readmission to acute care at 12 months post discharge (51% in the prolonged critical illness vs. 53% across all studies). Although in several studies, prolonged mechanical ventilation and duration of initial hospitalisation were identified as risk factors. This contrast may be due to the wide variation in how studies were reported; many studies in this analysis for example, did not quantify or report risk factors for readmission. Moreover, only a small number of studies reported discharge destination. Discharge destinations, for example long-term ventilation centres, may influence where, if and how a patient is readmitted back into acute care (if needed). There is a pressing need for more detailed work in this area, especially as COVID-19 patients often require prolonged ventilation and can spend extended periods of time in a critical care environment [110]. The recovery trajectory alongside detailed data on readmission risk will help support interventional work in this field.

Strengths of this review include a broad scope and detailed approach to analysis. There were, however, a number of limitations. First, our definition of prolonged critical illness was ventilated for, or a critical care stay of, > 7 days. Prolonged critical illness has a wide definition ranging from 3 to 21 days; as such our inclusion criteria may not be truly representative of this population [111, 112]. Second, we were unable to generate data from the studies around duration or nature of rehospitalisation, as these was not routinely or systematically reported across the studies. A further limitation is that the event (rehospitalisation) in most studies was identified via routinely collected, linked data. Coding practices in some countries are directly linked to payment; as such, hospital clinical practices in relation to readmission may be different. Coding of critical illness is also different internationally; in this review we included patients admitted to a critical care environment, as defined by the authors in each study. Other differences which may have impacted the reported results include the discharge destination in the prolonged critical care cohort. Long-term ventilation centres are found predominantly in the USA and thus the trajectory of this subgroup may differ internationally. Due to these issues, there may be significant heterogeneity in the cohorts included. Finally, the information available on the nature of critical illness was limited across the studies and thus the data extracted did not include, for example, exposure to mechanical ventilation or severity of illness. These important factors may have contributed to the need for subsequent healthcare.

Conclusions

Half of survivors of critical illness are readmitted to hospital within 12 months of critical care discharge. Patient characteristics such as comorbid status and frailty, initial acute hospitalisation course and nature, alongside illness-specific factors such as sepsis/re-infection were identified as risk factors for readmission. Future research should seek to understand the illness trajectory of patients following critical illness, with targeted interventions for those with pre-defined readmission risk factors.

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Figure legends

Figure 1: Flow diagram describing included excluded studies across the review process

Figure 2: Rate and timing of rehospitalisation. Random effect meta-analysis of proportions by rehospitalisation interval reported.

Figure 3: Rate and timing of rehospitalisation in long-term stay patients. Random effect meta-analysis of proportions by rehospitalisation interval reported.

Online Supporting Information

Table S1: Data summary

Table S2: Study quality assessment

Figure S1: Funnel plots visualising publication bias and heterogeneity across the studies included in the meta-analysis

Figure S2: Meta-regression outputs (including effect estimate plot)

Figure S3: Meta-analysis forest plot, with studies at high risk of bias removed

Appendix S1: Review search strategy

Appendix S2: Full statistical code

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CoCoPop framework used in the screening and review process		
Component	**Inclusions**	**Exclusions**
Condition	Readmission to acute care following discharge from hospital	Readmission to critical care within the same hospital period Primary care interactions
Context	All countries and types of acute hospital (district general teaching, tertiary referral) Any time period	Non- acute care setting healthcare interactions
Population	Patients admitted to an ICU or critical care environment	Studies in which less of than 50% of patients included had been exposed to a critical care/ICU environment Neonates/children

Table 1: Condition, context population (CoCoPop) summary of the approach to screening and review

Table 2: Characteristics of studies included in the full review. Values are number (proportion)

Study characteristic	**n = 87**
Geographical region	
USA	56.3 (49)
Canada	14.9 (13)
Europe	20.7 (18)
Asia	5.7 (5)
South America	1.2 (1)
Australia/New Zealand	1.2 (1)
Study type	
Cohort	92 (80)
Randomised controlled trial	4.6 (4)
Case control	3.4 (3)
Study scope	
Multicentre	55.2(48)
Single centre	44.8 (39)
Study population focus	
General ICU (including surgical ICU)	44.8 (39)
Acute respiratory distress syndrome	8.1 (7)
Sepsis/other specific infection	10.3 (9)
Long-term stay/ventilation (≥ 7 days)	11.5 (10)
Elderly patients	4.6 (4)
Cardiac ICU	9.2 (8)
Neurological ICU	2.3 (2)
Other	9.2 (8)
Time-points measured*	
< 30 days	1.2 (1)

30 days	31 (27)
60 days	3.5 (3)
90 days	12.6 (11)
6 months	9.2 (8)
12 months	28.7 (25)
> 12 months	24.1 (21)
Other	1.2 (1)

*studies could measure readmissions at multiple time-points

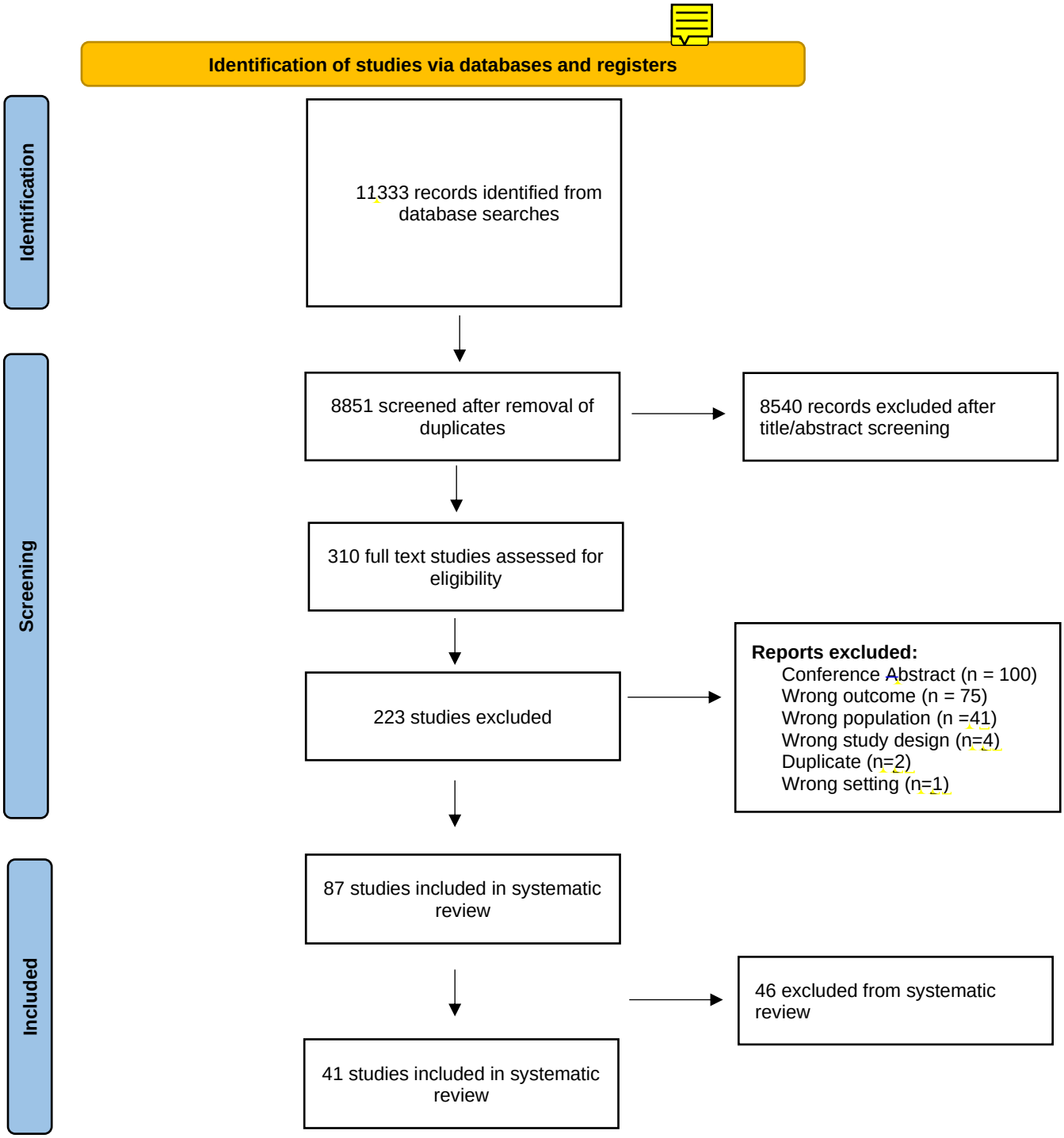
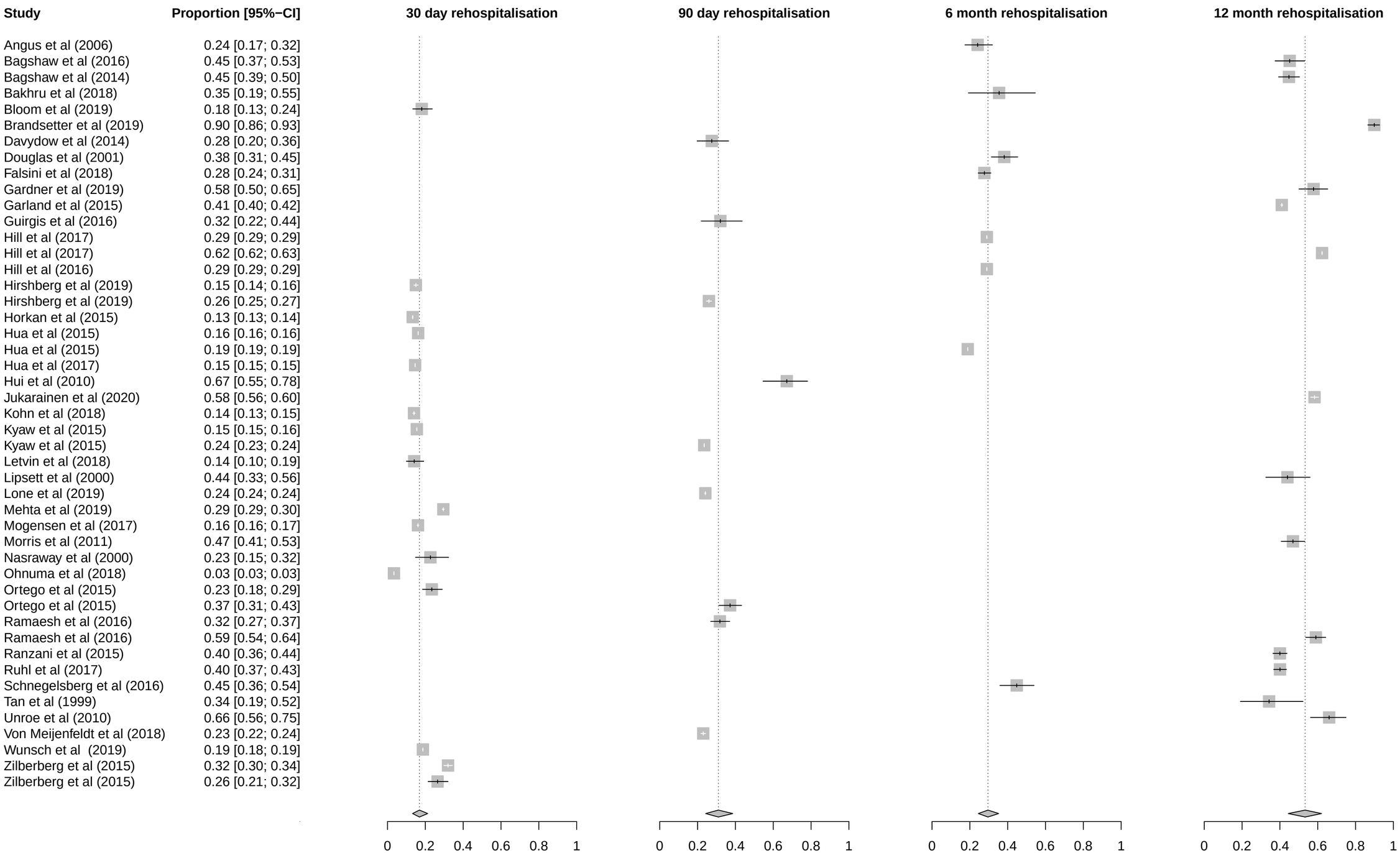


Figure 1: Prisma Flow Diagram



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