Scoping Review

Association between Sex and Mental Health Sequelae after ICU Discharge: A Scoping Review

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Background: Following discharge from intensive care units (ICUs), more than 50% of patients may develop mental health conditions including depression, post-traumatic stress disorder (PTSD), and anxiety. However, there is limited research to suggest risk factors.
Objective: Explore sex-related differences in the incidence, severity, and duration of mental health sequelae in adults after ICU discharge.
Methods: Studies published in English within the last 20 years, focusing on sex and mental health sequelae post-ICU. Online databases MedLine, EmBASE, Scopus, PsycINFO, and CINAHL were explored as of September 22, 2021.
Results: Of the 706 studies screened, six were included, and three demonstrated a statistically significant association between sex and mental health sequelae. Four outcomes of interest were noted: mental health-related quality of life (HRQoL), post-traumatic stress symptoms (PTSS), major depression/PTSD comorbidity, and major depression. Three studies that addressed mental HRQoL noted a decreased mental HRQoL in females compared to males, but two were statistically significant. No statistically significant association was found between sex and PTSS. One study examined both major depression/PTSD comorbidity and major depression and found a statistically significant association between female sex and both outcomes.
Conclusions: Despite methodological limitations of the identified studies, this scoping review shows a trend for worse mental health outcomes in females post-ICU. More research focusing on confounding factors is needed to better understand the associations between sex, gender, and mental health sequelae in post-ICU patients.

Keywords: Critical care, mental health, adults, sequelae, risk factors, PTSD, anxiety, depression, psychosocial, psychiatric, sex, gender, post-intensive care syndrome, quality of life, nursing

INTRODUCTION

Following discharge from intensive care units (ICU), it is common for patients to develop new physical, psychological, and cognitive impairments that affect their quality of life, a condition termed Post Intensive Care Syndrome (PICS) (Karnatovskaia et al, 2015). Mental health conditions post-ICU include depression, post-

traumatic stress disorder (PTSD), delirium, and anxiety, among others (Harvey, 2012). Although mental health consequences affect more than 50 percent of ICU survivors, little is understood surrounding the risk factors associated with this phenomenon (Karnatovskaia et al, 2015). Following discharge from the ICU, patients are vulnerable to mental health sequelae but are no longer under the direct supervision of trained health professionals (Harvey, 2012). Although the healthcare community is aware of such effects, there are few strategies in place to alleviate these consequences, and little research to suggest new possibilities for management (Harvey, 2012).

Evidence to date implies the existence of sexual dimorphism in critical illness outcomes, however, the degree to which males and females are differentially affected by post-ICU sequelae is unclear (Papathanassoglou et al, 2015). A research study conducted in Manitoba found that the male to female ratio of ICU admittance was 1.75 (Garland et al, 2013). Despite this difference, a cohort study conducted in Sweden concluded that females who survive intensive care have more psychological difficulties than males (Schandl et al, 2012). In contrast, another study from the United States found that the female sex did not have a higher risk of PTSD symptoms following ICU discharge (Davydow et al, 2009).

Though some studies suggest there may be a relationship between sex and post-ICU outcomes, they have yielded inconsistent results (Davydow et al, 2009; Schandl et al, 2012). Moreover, the perception of stress and coping mechanisms, as well as longer-term effects of stress, appear to be sex-specific with rates of PTSD, panic disorder, and major depression being higher in females (Bangasser & Wieesielis, 2018). Still, less is known about the association between sex and the incidence and experience of mental health sequelae post-ICU. Although sex is understood as a significant determinant of health, it has been largely ignored by critical care research (Papathanassoglou et al, 2015). To our knowledge, no published review to date has addressed the effect of sex on mental health outcomes after hospitalization in an ICU.

Rationale

Studies across both North America and Europe have shown that those admitted to ICUs are predominantly male (Garland et al, 2018; Hill et al, 2019). It has been proposed that this difference is accounted for by higher rates of critical illnesses in males compared to females (Garland et al, 2018). Furthermore, differences were found throughout the treatment courses of those in the ICU as well; males were more likely to be diagnosed with

hyperactive delirium while in the ICU, as well as to be treated with atypical antipsychotics (Garland et al, 2018). They also experienced more severe cognitive impairment after ICU discharge, despite the proportion of women experiencing cognitive impairments being higher (Karamchandani et al, 2018). It is possible that sex may account for differences at every stage of the critical illness trajectory, including admission, care while on the unit, and post-discharge (Garland et al, 2018; Karamchandani et al, 2018; Son et al, 2020). Given this data, we hypothesize that there may likely be a difference in the mental health sequelae following ICU discharge.

Objectives

Our review aims to identify and synthesize existing research evidence regarding the association between sex and mental health sequelae in ICU survivors in an effort to inform future research and clinical practice. Specifically, we investigated potential associations between sex and the incidence, severity, duration, and type of psychiatric sequelae in adults after discharge from ICU. The secondary objective of this study is to highlight potential gaps in the literature and methodological implications for future studies.

METHODS

Protocol and Registration

Our pre-planned protocol was registered with the Open Science Framework. Registration DOI:10.17605/OSF.IO/KB2XC

Ethics

This scoping review does not require ethics approval because it relies exclusively on summarizing and synthesizing published anonymized data. The process of data extraction did not generate identifiable information, it does not involve any intervention by researchers, and the data are publicly available (TCPS2, 2018).

Eligibility Criteria

We targeted published peer-reviewed primary studies, which explicitly included an exploration of the mental health of ICU survivors, including symptoms and diagnoses. Grey literature and secondary studies were not included in our study. Further, interventional studies were not included because our focus is on the presentation of mental health morbidity.

Information Sources

Literature searches were conducted in consultation with a content-expert librarian at the University of Alberta. MedLine via OVID (1964-present), EmBASE via OVID (1974 -present), Scopus (1960 - present), PsycINFO via OVID (1806 - present) and CINAHL via EBSCO (1937- present) were

explored using our search strategy.

Search

A sample of the full search strategy used in the MEDLINE database has been included in the Appendix 1.

Selection of Sources of Evidence

Screening of the articles was conducted using Covidence, an online systematic review manager software, through the University of Alberta. (Veritas Health Innovation, 2019). Two independent reviewers screened articles for inclusion and exclusion criteria, as outlined in Table 1, to determine which studies would be used for data extraction. Next, reviewers screened the title and abstract of all studies and tagged them as "yes," "no," or "maybe," based on the inclusion and exclusion criteria. Studies marked "no" by both reviewers were excluded, and any discrepancies between reviewers' decisions were solved via consensus between the reviewers and a clinical expert (EP). Articles that were not marked "no" by either reviewer were included in a full-text screening to further ensure they meet the inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart diagram (Page et al, 2021) as shown in Figure 1 summarizes the entire study selection and screening process.

Data Elements Extracted

During this stage, relevant data were extracted from the included studies to provide a high-level summary of study findings. Data elements and extraction methods were mutually agreed upon by all members of the research team and were pilot tested and refined with a subset of the identified studies. Charting was used to effectively determine which variables will be relevant in answering the research question (Levac et al, 2010). Our extracted data included: Author (s), year of publication, study location and type of ICU, study design, aims/ objective, characteristics of participants, time since ICU discharge, sample size, percentage of males/females in the sample, sex-related differences, or effects, time-lapse between ICU discharge and presentation of mental health conditions, types of mental health morbidity, presence of adjustment of pre-ICU mental health conditions, and other confounders.

Critical Appraisal of Individual Sources of Evidence

A critical appraisal of each study is used to appreciate the studies' merits and outline the most relevant studies. Critiquing studies for risk of bias has been shown to contribute and to cause inconsistency in scoping reviews (McDonagh et al, 2013). We assessed the quality of identified studies using the applicable Joanna Briggs Institute critical appraisal tools (Joanna Briggs

Institute [JBI], 2017a; JBI, 2017b) and Mixed Methods Appraisal Tool (Hong et al, 2018). No studies were excluded based on quality.

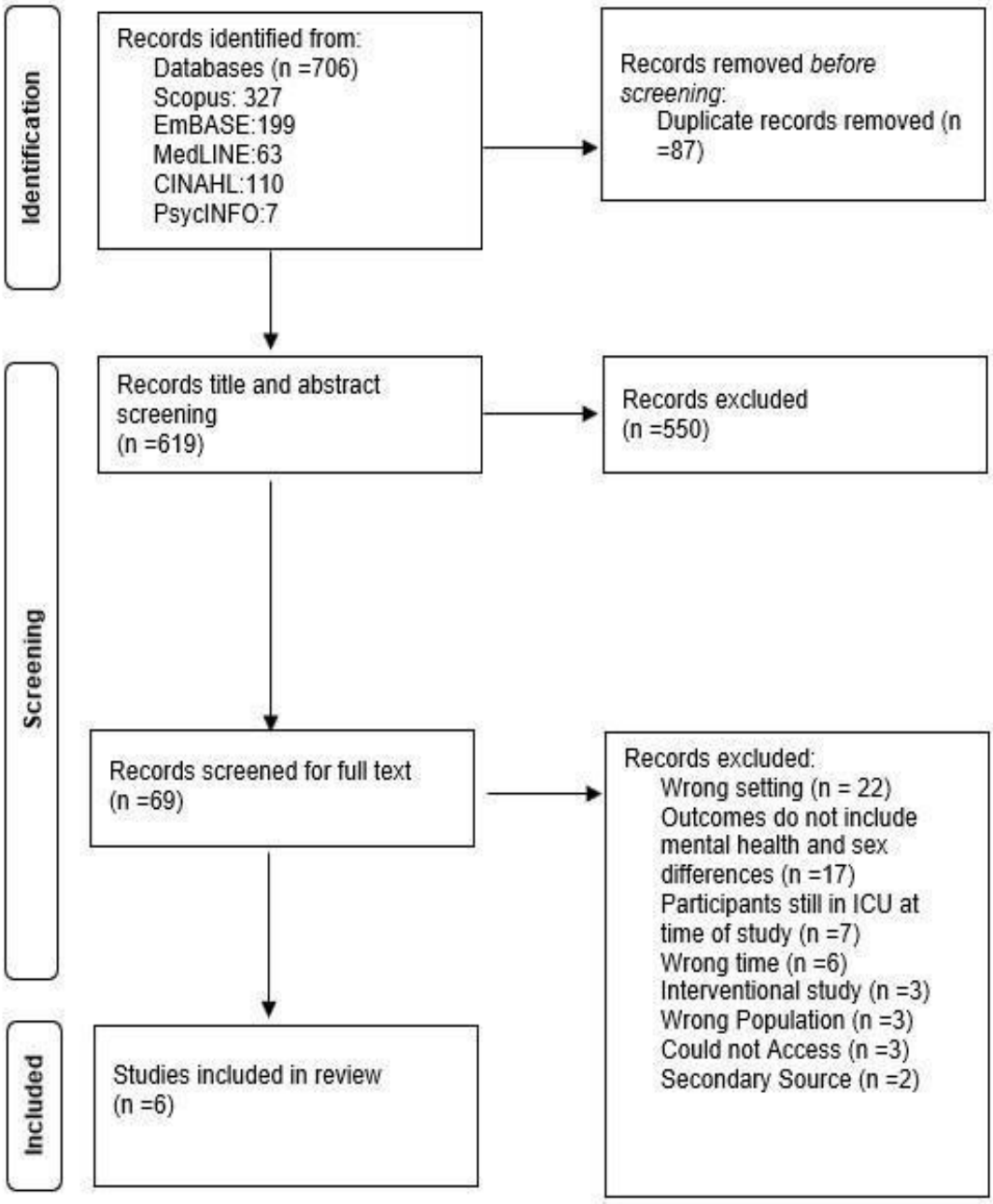
Table 1.

Inclusion Criteria and Exclusion Criteria for Scoping Review

	Inclusion Criteria	Exclusion Criteria
Study type	Primary, empirical	Secondary sources of any kind (literature reviews, editorials, etc.)
Reference type	Peer-reviewed studies published during or after 2001	Gray literature
Primary study outcomes	Mental health sequelae following discharge from an ICU Studies that focus on sex differences or effects of sex on mental health post-ICU	Non-mental health sequelae Studies looking at psychiatric morbidities that existed prior to discharge Studies looking at participants who have not been admitted to an ICU Interventional studies
Language	Studies published in English	Studies published in languages other than English
Setting	Any location an individual may have been discharged to following their ICU stay (rehabilitation, medical units, home, long term care, etc.)	ICUs
Participants	Individuals who were once admitted to an ICU, and have since been discharged to any location Individuals over the age of 18	Individuals still in ICU at the time of the study Individuals who were never admitted to an ICU Individuals under the age of 18

Figure 5

Selection Process of the Identified Studies. PRISMA Flow Diagram adapted from PRISMA 2020 Statement: An Update Guideline for Reporting Systematic Reviews



Data charting and synthesis

In analyzing the data, we provided a numerical and thematic summary and synthesis of the data. Data analysis and synthesis were used in reporting the results step to articulate the findings to readers and to highlight any gaps in the literature, as well as methodological shortcomings of this body of literature. Lastly, we discussed the clinical and research implications of the data.

RESULTS

Selection of sources of evidence

Our search was conducted on June 6, 2021, and updated on September 22, 2021. A total of 706 papers were identified from the five databases (MEDLine: 63, EmBASE:199, Scopus: 327, PsycINFO: 7, CINAHL: 110). After the removal of duplicates, two independent reviewers screened 619 titles and abstracts. Of these, 550 were excluded and 69 studies were full text-screened. We were unable to access the full text of three studies, and an additional 60 studies were excluded, leaving 6 studies to be included. No studies were identified through hand searching. See Figure 1.

Characteristics of Sources of Evidence

The six included studies' authors, location, designs, objectives, and main findings related to this study are presented in Table 2. Studies were published between 2011-2020 in English, and vary in geographical location, with one study from France (Wawer et al, 2020), one study from Greece (Asimakopoulou & Madianos, 2014), one from Scotland (Griffith et al, 2018), two from Australia (Talisayon et al, 2011; McKinley, 2016), and one international multicentric study (Bohm et al, 2019). The main inclusion criteria for the included studies were participants 18 years or older, admitted to an ICU. In the identified studies, data were collected between 1 week and 12 months after discharge (Asimakopoulou & Madianos, 2014; Bohm et al, 2019; Griffith et al, 2018; McKinley, 2016; Talisayon et al, 2011; Wawer et al, 2020). Only Griffith et al. (2018) revisited participants at multiple intervals (6 and 12 months after discharge). All studies had more male than female participants. Only one study, Asimakopoulou and Madianos (2014), explicitly states the time-lapse between ICU discharge and presentation of mental health sequelae.

Table 2.

Study Characteristics and Main Findings (A) Setting, design, objectives, participant characteristics; (B) Diagnoses, time since ICU discharge, sample, mental health assessment tools; (C) Sex related differences, time-lapse to first symptoms, adjustment, confounders.

A.

Authors; Publication Date; Study Location	Setting	Study Design	Study Objectives	Participant Characteristics
Asimakopoulou & Madianos; 2014; Greece (Greater Athens)	5 ICUs across Athens, Greece	Cross-sectional study and Case control	Prevalence of major depression and PTSD among ICU patients	18 - 70 years; ICU admission ward for more than 24 h
Bohm et al.; 2019; Europe and Australia	36 ICUs across Europe (Czech Republic, Denmark, Italy, Luxembourg, Netherlands, Norway, Sweden, Switzerland, United Kingdom) and Australia	Post-hoc cross-sectional study	Investigate differences in HRQoL in survivors of the TTM study	18+ years, resuscitated from an out of hospital cardiac arrest, who had a GCS of less than 8 after more than 20 minutes of ROSC
Griffith et al.;2018; Scotland (Edinburgh)	2 ICUs	Nested prospective cohort study within randomized trial	Cohort level trajectories of PCS and MCS between 3 and 12 months after ICU discharge; Factors were most strongly associated with HRQoL at 6- and 12-months post ICU discharge	18+ years, ICU survivors who required more than 48 hours of mechanical ventilation
McKinley; 2016; Australia (Sydney, Royal North Shore Hospital)	3 ICUs	Prospective observational study; part of larger cohort study	Describe HRQoL of critically ill patients treated in an ICU and identify factors associated with the HRQoL 6 months after discharge	18+ years; ICU length of stay of 2 or more nights
Talisayon et al.; 2011; Australia (Sydney)	ICUs in a hospital in Sydney, Australia	Mixed methods	Prevalence and severity of symptoms of PTS in patients who have been mechanically ventilated in ICU	18+ years; mechanically ventilated for more than 24 hours, and in the ICU for 48 hours or longer
Wawer et al.;2020; France (Lyon)	3 ICUs at a French University Hospital	Prospective cohort study	Diagnostic accuracy of the IES-R assessed within 8 days following the ICU discharge, to predict presence of PTSS at 3 months. Explore risk factors for PTSS at 3 months.	18+ years, hospitalization greater than or equal to 2 nights in the participating ICU, transfer to a ward of the Lyon university hospitals, and agreement to participate

B.

Authors; Publication Date; Study Location	Types of ICU Admission Diagnoses (%)	Time Since ICU Discharge	Sample Size; Male (n/%) to Female (n/%)	Mental Health Assessment Tools
Asimakopoulou & Madianos; 2014; Greece (Greater Athens)	Multitrauma (36.3%), Autoimmune disease (2%), Surgical disease (8.8%), Pathological disease (10.8%), Oncological (10.8%), Cardiovascular disease (2.9%), Infection disease (9.8%), Pulmonary disease (8.8%), Bleeding (7.8%), Burn (2%)	3 months	102; (65/63.7%) :(37/36.27%)	MINI; Major depression and PTSD
Bohm et al.; 2019; Europe and Australia	Out of hospital cardiac arrest (100%)	180 days	442, 440 complete responses, 31 answered by proxy; (374/84.6%) :(68/15.38%)	SF-36; HRQoL
Griffith et al.; 2018; Scotland (Edinburgh)	Respiratory (35%), Cardiovascular (29%), Gastrointestinal (25%), Miscellaneous (2%), Neurologic (5%), Renal (1%), Trauma (3%)	6 months; 12 months	165 at 6mo., 155 at 12mo.; Unknown; of parent study sample = (137/57%): (103:42.95%)	SF-12; HRQoL
McKinley;2016; Australia (Sydney, Royal North Shore Hospital)	Cardiovascular (43%), Respiratory (6.2%), Gastrointestinal (8.3%), Neurological (22.3%), Trauma (8.8%), Sepsis (2.1%), Other (9.3%)	6 months	193; (125/64.7%): (68/35%)	SF-36; HRQoL
Talisayon et al.;2011; Australia (Sydney)	Cardiovascular (25.8%), Gastrointestinal (22.7%), Trauma (8.2%), Respiratory (21.6%), Other (21.6%)	1 week	97 completed IES; 5 of those participants completed interviews.; (58/59.8%): (39/40.2%)	IES; PTSS
Wawer et al.;2020; France (Lyon)	Surgical (52%), Medical (29%), Trauma (19%)	3 months	145; (106/73%): (39/27%)	IES-R; PTSS

C.

Authors; Publication Date; Study Location	Sex-Related Differences	Time-lapse between ICU discharge and presentation of mental health conditions	Adjustment of pre-ICU mental health condition	Other confounders
Asimakopoulou & Madianos; 2014; Greece (Greater Athens)	24.6% of males and 45.9% of females in the ICU group met criteria for major depression (OR = 4.93; 95% CI =1.6-15.7; p = 0.005); 12.3% of males and 27.0% of females met criteria for both major depression and PTSD (OR = 11.99; 95% CI = 2.36-60.83; p = 0.003)	Cases developed prior to the interview; "weeks after discharge"	Majority of subjects provided contradictory answers when asked	-

Bohm et al.; 2019; Europe and Australia	Females had significantly lower scores in MCS compared to males (MCS 47.4 (95% CI = 44.6-50.2) vs 50.4 (95% CI = 493. -51.5), p = 0.03);	Not reported	Did not measure pre-arrest status	Cohorts dominated by males and the smaller percentage of females may have affected the result.
Griffith et al.; 2018; Scotland (Edinburgh)	At 6 months, bivariate linear regression yielded 95% CI = -2.65 to 5.40, beta of 1.37, and p = 0.502; at 12 months, bivariate linear regression yielded 95% CI = -3.27-4.31, beta of 0.52, and p = 0.787	Not reported	From parent study sample, 32% had depression and 26% had an anxiety or panic disorder	Male to female proportions were of the original sample of 240 participants
McKinley;2016; Australia (Sydney, Royal North Shore Hospital)	SF-36 mental component: mean (SD) female 45.58 (11.75), male 49.66 (10.73); p = 0.01	Not reported	Not reported	-
Talisayon et al.;2011; Australia (Sydney)	Higher scores observed in females, not significant. Bivariate analysis yielded X^2 = 3.763, p = 0.052; Multiple linear regression yielded unstandardised coefficient (B) = 4. 803, standard error of B = 3.686, 95% CI = -2.516-12.122, p = 0.196	Not reported	Did not include patients with a history of mental illness or noncompliance with care/treatment in the study	-
Wawer et al.;2020; France (Lyon)	Univariate Analysis for female sex; (OR = 1. 71, 95% CI = 0.62-4.73, p = 0.31)	Not reported	64% of patients assessed at 8 days and 3 months had a mental health history	Did not explicitly collect data relating IES scores with sex; majority of patients had psychiatric history

Note. Mini International Neuropsychiatric Interview, (MINI), Post-Traumatic Stress Disorder (PTSD), Post-Traumatic Stress Symptoms (PTSS), Intensive Care Unit (ICU), Health-Related Quality of Life (HRQoL), Target Temperature Management (TTM), Glasgow Coma Scale (GCS), Impact of Events Scale (IES), Impact of Events Scale-Revised (IES-R), Short Form Survey- 36 (SF-36), Short Form Survey- 12 (SF-12), Odds Ratio (OR), Confidence Interval (CI)

Types of Methods and Design

Of the six studies included in our review, five have used quantitative methods (Asimakopoulou & Madianos, 2014; Bohm et al, 2019; Griffith et al, 2018; McKinley, 2016; Wawer et al, 2020) and one mixed method (Talisayon et al, 2011). Only the quantitative data from the mixed methods study were included in our results because no sex-related analysis of the qualitative data was conducted.

Among the five quantitative studies, three were cohort studies (Griffith et al, 2018; McKinley, 2016; Talisayon et al, 2011; Wawer et al, 2020), one was a cross-sectional case-control study (Asimakopoulou & Madianos, 2014), and one was a post-hoc analysis of data from a randomized clinical trial (Bohm et al, 2019). The prospective cohort study was also nested within a randomized controlled trial. Both studies included patients from both interventional and non-interventional cohorts of their respective randomized control trials, as no health-related quality of life differences were found between groups.

Types of Outcome Measures and Tools

Three of the reviewed studies measured health-related quality of life (HRQoL) using variations of the Medical Outcomes Study Short Form Survey (Bohm et al, 2019; Griffith et al, 2018; McKinley, 2016). Two studies used the 36-Item Short Form Survey (SF-36; Bohm et al, 2019; McKinley, 2016), while one opted to use the shortened version, the 12-Item Short Form Survey (SF-12; Griffith et al, 2018). The SF-36 measures quality of life, including a physical component summary (PCS) and a mental component summary (MCS). For the purpose of this review, we examined only the MCS scores of the studies utilizing this measurement tool. The MCS includes, in varying degrees, each of the eight scales in the SF-36, including physical measurements. One study used an instrument based on MINI and DSM-IV where only PTSD and major depression was accounted for in this study (Asimakopoulou & Madianos, 2014). Finally, two studies used the Impact of Event Scale (IES), which measures the frequency of avoidance and intrusive symptoms concerning a specific event (Talisayon et al, 2011; Wawer et al, 2020). All tools exhibited adequate psychometric properties. One of the studies included the Depression, Anxiety and Stress Scales - 21 and the Post-Traumatic Stress Disorder Checklist for a Specific Event, however, sex-specific data were not provided for these tools and thus the data were not extracted (McKinley, 2016).

Critical Appraisal of Evidence

No studies were excluded based on their appraisal results per scoping

review methodology, and to avoid disregarding relevant findings (see Appendix 2-4). Each cross-sectional study and the mixed methods study met all quality appraisal criteria. As for the cohort studies, some methodological gaps were noted. Griffith et al. (2018) did not provide adequate data regarding the sample included in their study, and instead mostly presented data regarding the parent study, which may or may not apply to their analyses. Furthermore, we were unable to access their data regarding loss of follow-up. McKinley (2016) also did not address attrition at follow-up.

Further, most of the studies did not address the time between the presentation of mental health sequelae and ICU discharge, nor did most explicitly address the existence of mental health conditions before ICU admission. These confounders may have affected participants' decisions to participate and remain with the study, and the validity of the data presented.

Results of Individual Sources of Evidence

Our summary table provides a comprehensive review of the results from each source (Table 2). The combined number of participants from each study was n=1,144, with five of the studies reporting response rates. Response rates ranged from 56%-90% (see Appendix 5). Of the pooled sample of participants in the identified studies, sex was reported for only 979 participants (85.6%), of which 728 were male (74%), and 251 (26%) were female. Across the included studies, participants' ages ranged from 27 to 77 years old, with 60 years as the average age.

The predominant ICU admission diagnosis was for cardiovascular disease, highest in Talisayon et al, (2011) (25.8%), and McKinley, (2016) (43%). Of the included studies, none specifically discussed the time-lapse between ICU discharge and the presentation of mental health morbidities. Only Asimakopoulou and Madianos (2014) identified that cases of depression appeared an unspecified number of weeks after discharge. Five out of six of the studies included assessed mental health symptoms, while one more formally evaluated diagnostic criteria (Bohm et al., 2019; Griffith et al, 2018; McKinley, 2016; Talisayon et al, 2011; Wawer et al, 2020). Although the tools discussed mental health diagnostic criteria, none of the participants were given an official mental health diagnosis by a health professional.

Each of the studies examining HRQoL found females to have a lower MCS score (Bohm et al, 2019; Griffith et al, 2018; McKinley, 2016), however, this difference was significant in two out of three studies (Bohm et al, 2019; McKinley, 2016). The third study examining HRQoL did not provide scores

but found sex to not be a risk factor through a bivariate linear regression in a sample of 97 post-ICU patients (Griffith et al, 2018). Studies discussing post-traumatic stress symptoms did not find a significant association between sex and mental health outcomes (Talisayon et al, 2011; Wawer et al, 2020). One study found a significant association between female sex and both PTSD/major depression comorbidity and major depression (Asimakopoulou & Madianos, 2014). Only two of our included studies addressed pre-ICU mental health conditions with data on types of psychiatric disorders (Talisayon et al, 2011; Asimakopoulou & Madianos, 2014). Additionally, Talisayon et al. (2011) explicitly excluded participants with mental illnesses, and Asimakopoulou and Madianos (2014) collected brief narrative data on psychiatric symptoms. Below we present findings by the outcome of interest.

Summary of Major Outcomes

Mental Health Component of Health-Related Quality of Life (HRQoL)

Findings related to sex differences and HRQoL were mixed. While Bohm et al. (2019) and McKinley (2016) found that female sex was significantly associated with poorer HRQoL, Griffith et al. (2018) did not identify sex as a risk factor. Through logistic regression, Bohm et al. (2019) reported that in the MCS, males scored an average of 50.4, with a 95% confidence interval (CI) of 49.3-51.5, while females scored an average of 47.4 (95%CI = 44.6-50.2, $p = 0.03$). McKinley (2016) also noted that while males scored an average of 49.66 (SD = 11.75), females scored lower, with an average of 45.59 (SD = 10.73; $p = 0.01$). Although Griffith et al. (2018) did not compare the raw MCS scores of men and women, through a bivariate linear regression, Griffith et al. (2018) found a beta of 1.37 (95% CI = -2.65- 5.40) at 6 months, and a beta of 0.52 (95% CI = -3.27-4.31) at 12 months ($p > 0.05$), which suggests no statistically significant correlation between sex and HRQoL. However, no adjustment for confounders was used in that study.

Post-Traumatic Stress Symptoms (PTSS)

By using the Impact of Events Scale tool, both Talisayon et al. (2011) and Wawer et al. (2020) did not find a significant association between sex and PTSS. Although Talisayon et al. (2011) acknowledge finding higher scores in females, a multiple linear regression model yielding a beta of 4.803 (95% CI = -2.516-12.122, $p = 0.196$) did not find sex to be a significant predictor of PTSS. Likewise, univariate analysis by Wawer et al. (2020) identified an odds ratio of 1.71 (95% CI = 0.62-4.73, $p = 0.31$), not supporting sex as a significant factor in PTSS post-ICU.

Major Depression/Post-Traumatic Stress Disorder Comorbidity

Asimakopoulou and Madianos (2014) found female sex to be significantly associated with major depression and major depression/PTSD comorbidity in ICU survivors. In their sample, 24.6% of males and 45.9% of females met diagnostic criteria for major depression, and 12.3% of males and 27% of females for major depression/PTSD. A logistic regression model revealed female sex to be a statistically significant risk factor of major depression (OR = 4.93, 95% CI = 1.6-15.7, p = 0.005), and major depression/PTSD (OR = 11.99; 95% CI = 2.36-60.83, p = 0.003).

DISCUSSION

Our search resulted in only six studies meeting the inclusion criteria for assessing association between sex and mental health sequelae after ICU discharge, clearly highlighting the need for additional research. Further, the current literature is heterogeneous regarding outcome measures as PTSD, major depression, major depression-PTSD comorbidity, PTSS, and HRQoL have been assessed in different studies. With Asimakopoulou and Madianos (2014) as an exception, most studies referred to depression and anxiety, but these terms were in reference to symptoms, rather than clinical diagnoses. Our study aimed to investigate potential associations between sex and the prevalence, severity, duration, and type of psychiatric sequelae. However, the available studies only provided data regarding prevalence. These further highlight both the need for more research as well as for consistent outcome measures to explore risk factors associated with mental health sequelae post-ICU.

Health-Related Quality of Life

A few factors may account for the mixed results regarding the association between HRQoL post-ICU and sex. While Bohm et al. (2019) and McKinley (2016) assessed participants 180 days and 6 months post-ICU, respectively, Griffith et al. (2018) assessed participants at both the 6 and 12-month mark post-ICU. At this point it is not clear if sex may be a factor in earlier versus delayed onset of psychiatric sequelae after ICU discharge, therefore, more investigation is needed to clarify this. Consequently, although Griffith et al. (2018) included appropriate follow-up, it is unclear if the results of their study at 12-months can be effectively synthesized with the other studies investigating HRQoL closer to the ICU experience.

In addition, these studies used the Mental Component Summary of varied Short Form Surveys to gauge mental health effects. Bohm et al. (2019) and McKinley (2016) used the 36- question version (SF-36) and Griffith et al. (2018) used the 12-question version (SF-12). Although the Short Form

Survey is an approved tool for assessing HRQoL, this tool is designed such that the PCS and MCS results are interdependent, so the validity of using MCS in isolation to assess mental health is questionable. Therefore, although the results for Bohm et al. (2019) and Griffith et al. (2018) may be statistically significant, these results are difficult to interpret as a valid independent measure of mental health outcomes.

The disproportionately lower numbers of females included in the samples may also have introduced bias, obscuring the relationship between sex and psychiatric sequelae. Moreover, some studies have targeted conditions that are more prevalent in men. For example, Bohm et al. (2019) only included participants who experienced out-of-hospital cardiac arrest, meaning that their results are not representative of the general ICU population. This also influences the sex distribution of the samples, as the incidence of out-of-hospital cardiac arrest is higher in men (Kim et al, 2001). This is evident in Bohm et al. (2019) as they report their sample to be 84.6% male. However, Bohm et al. (2019) reported that females had worse mental health outcomes. Unequal sex distribution in the samples may also be due to the fact that admission in critical care seems to be higher in men and that many investigators have focused on populations with cardiovascular diagnoses, which are known to be higher in males (Maas et al, 2010). Further, males have consistently found to have higher rates of admission, with 67% of admission being male patients, as well as experiencing higher readmission and length of stay (Zettersten et al, 2019). Bohm et al.'s (2019) sample appears to have disproportionately more males (84.6%) compared to the general ICU population, making it difficult to truly examine sex differences.

Despite skewed samples and the aforementioned limitations, overall, the reviewed data show a trend for lower mental health-related quality of life post-ICU in females compared to male survivors. However, due to the confounders and limitations of assessment tools and follow-up, this conclusion cannot be generalized and warrants further investigation. Future research should address the validity of tools, gender distribution, and evidence-informed follow-up periods.

Post-Traumatic Stress Symptoms

Unlike PTSD, PTSS refers to a group of symptoms rather than a diagnosis. Specifically, PTSS refers to experiences of intrusion, avoidance, and hyperarousal symptoms following a traumatic event (Talisayon et al, 2014; Wawer et al, 2011). On the other hand, PTSD in Asimakopoulou and Madianos (2014) measures symptoms according to the Diagnostic and

Statistical Manual (DSM-IV). While the identified studies did not show statistically significant associations between post-traumatic stress scores and gender, several confounders need to be taken into account. For example, it is unclear if the timing of post-ICU follow-up was sufficient for the development of post-traumatic symptomatology, and if sex might have been a factor in the time of onset. Specifically, Talisayon et al. (2011) examined symptoms one week after discharge, the shortest period of all the included studies. Given the short timeline, this study potentially missed participants who later developed PTSS.

Furthermore, it is unclear if the prevalence of pre-existing mental health conditions in each study is representative of the ICU population, and therefore external validity is dubious. Talisayon et al. (2011) and Wawer et al. (2020) examined samples with 0% and 64% of participants presenting with mental health history before ICU admission, respectively. In the case of Wawer et al. (2020), utilizing a sample in which the majority presents with pre-existing mental health conditions introduces a major confounder in deciphering the relationship between sex and mental health after the ICU.

Post-Traumatic Stress Disorder and Depression

According to Rief et al. (2004), females in the general population are twice as likely to experience depression than males. However, Asimakopoulou and Madianos' (2014) research findings suggest that following ICU discharge, females are five times more likely to experience major depression, with a very wide confidence interval of this estimate, reaching as high as 15 times more likely. Similarly, females showed an almost 12-fold higher risk of major depression/PTSD post-ICU, but again with a very wide confidence interval attesting to the large variability and error in the sample. Furthermore, the majority of participants provided contradictory answers regarding their mental health history and therefore the effects of pre-existing conditions are not predictable.

Response Rates

Despite a response rate of 73%, it is possible that the studies do not show an accurate view of the population. Potentially, those who were inflicted with the most or least severe mental health sequelae might have declined to participate, and this may have biased the results. Response rates may have also been affected by demographic factors such as the sex of the responders, acting as a source of bias. For instance, each study presented a majority male sample, indicating sex and/or gender-related differences in response rates. Traditional gender roles may affect response rates as

women are generally expected to provide care to others and may not have decided to address their mental health via these studies. On the contrary, men are less supported in expressing mental health issues, which may have discouraged them from participating or even accurately reporting the severity of their mental health sequelae. More research is required to explore the intricacies of these variables, especially the effect of a spectrum of gender roles beyond the traditional binary approach, on mental health outcomes after ICU hospitalization.

Limitations

Due to time constraints, no hand searches or grey literature were included in our study. Further, we were unable to access some studies that we may have otherwise included. A librarian with the initials BG from the University of Alberta was contacted and was not able to access the missing studies. For these reasons, we may not have searched the entire extent of the available literature on this topic and could be missing relevant data. Another limitation is the inclusion of studies published in English only, which might have excluded relevant data in other languages. Finally, the review incorporated literature published only as of September 2021, and possibly misses relevant literature published after this date.

Since our study explored international ICUs, different hospitals, and geographical locations which could impact whether a condition would warrant an ICU admittance. This could mean that in some cases, not all patients who are critically ill are admitted to the ICU or could be receiving ICU-level care in a different environment and would thus not be included in such studies. Therefore, since our study did not define specific diagnoses or severities of illness to include, and instead focused on location, we may have missed valuable data regarding the mental health sequelae of critically ill patients in settings other than ICU.

Our main concern for the data searching process was the fluid use of the terms sex and gender in literature. According to the Canadian Institutes of Health Research (2015), the word sex refers to biological characteristics, however, gender seeks to acknowledge the societal definitions of what is masculine or feminine. When these studies refer to "(wo)men" or "(fe)male" it is unclear whether they are being applied according to currently accepted definitions. For our purposes, we included studies that used the terms specifically, interchangeably, or did not specify definitions.

CONCLUSION

The lack of significant and consistent evidence on the association between

sex and mental health sequelae after ICU discharge suggests a gap in the literature and the need for further research and investigation. This scoping review aimed to identify and synthesize existing research evidence regarding the association between sex and mental health sequelae in ICU survivors, in an effort to inform future research and clinical practice.

Having a better understanding of the risk factors for these mental health effects will allow practitioners to equip their patients with the resources necessary to reduce these effects, meaning social workers, occupational and physical therapists, nutritionists, psychologists, and other allied health professionals may play a role in reducing the mental health effects of discharged patients.

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Appendix 1.

Search Strategy Table

#	Search Statement	Results
1	Sex characteristics/	57576
2	Sex Factors/	273894
3	(sex* or gender* or male* or female* or m#n or wom#n).m_titl.	867559
4	1 or 2 or 3	1098280
5	intensive care units/ or burn units/ or coronary care units/ or respiratory care units/	68689
6	Critical care/	56075
7	exp Critical Illness/	33432
8	Survivors/	26353
9	("coronary care unit*" or "critic* care unit*" or "intens* therap* unit" or "intens* treat* unit" or "high depen* unit").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12009
10	(icu or ccu or cicu or micu or cvicu or sicu or ticu or itu).m_titl.	10653
11	(intens* care adj4 unit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	110975
12	(intens* adj4 care unit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	111129
13	(intens* care unit adj2 survivor).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13

14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	232338
15	patient discharge/ or patient transfer/	42030
16	("patient discharge" or "post discharge" or "post-discharge" or "hospital discharge" or "icu discharge" or "after discharge").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	80623
17	15 or 16	88696
18	14 and 17	9709
19	mental competency/ or mental health/ or posttraumatic growth, psychological/ or resilience, psychological/ or exp mental disorders/	1359415
20	exp Stress Disorders, Post-Traumatic/ or exp Stress Disorders, Traumatic/ or exp Stress, Psychological/	177965
21	psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/	37329
22	Depression/	132303
23	("post intensive care syndrome" or "post sepsis syndrome" or "post-icu syndrome" or "pics" or "pss" or "icu-acquired weakness" or "intensive care unit acquired weakness").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13068
24	("depress*" or "stress*" or "distress*" or "syndrome*" or "suicid*" or "sleep*" or "disorder*" or "mood*" or "anxiety*" or "panic*" or "obsessive-compuls*" or "obsessive compuls*" or "deliri*" or "delus*" or "hallucinat*" or "psychotic*" or "paranoi*" or "mania" or "maniac*" or "compuls*" or "phobia*" or "neurot*" or "neuros*" or "irrita*" or "fatigue*" or "tired*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5183913
25	("cognitive morbid*" or "cognitive well*" or "cognitive condition*" or "cognitive state*" or "cognitive difficult*" or "cognitive problem*" or "cognitive disorder*" or "cognitive* distress*" or "cognitive* balance*" or "cognitive* imbalance*" or "cognitive* unbalance*" or "cognitive* capa*" or "cognitive* incapa*" or "cognitive* impair*" or "cognitive* dysfunc*" or "cognitive defici*" or "cognitive* healt*" or "cognitive ill*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism	124024

	supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
26	("psych* morbid*" or "psych* well*" or "psych* condition*" or "psych* state*" or "psych* difficult*" or "psych* problem*" or "psych* disorder*" or "psych* distress*" or "psych* balance*" or "psych* imbalance*" or "psych* unbalance*" or "psych* capa*" or "psych* incapa*" or "psych* impair*" or "psych* dysfunc*" or "psych* defici*" or "psych* healt*" or "psych* ill*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	216758
27	("mental morbid*" or "mental well*" or "mental condition*" or "mental state*" or "mental difficult*" or "mental problem*" or "mental disorder*" or "mental distress*" or "mental balance*" or "mental* imbalance*" or "mental* unbalance*" or "mental capa*" or "mental incapa*" or "mental impair*" or "mental dysfunc*" or "mental defici*" or "mental healt*" or "mental ill*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	423303
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	5619055
29	4 and 18 and 28	79
30	limit 29 to (english language and humans and yr="2001 -Current" and "all adult (19 plus years)")	63

Appendix 2.

Quality Appraisal Results Using the Joanna Briggs Institute Checklist for Analytical Cross-Sectional Studies

Study	**Asimakopoulou & Madianos (2014)**	**Bohm et al., (2019)**
Were the criteria for inclusion in the sample clearly defined?	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Yes
Were objective, standard criteria used for measurement of the condition?	Yes	Yes
Were confounding factors identified?	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes

Digital Content 3.

Quality Appraisal Results Using the Joanna Briggs Institute Checklist for Cohort Studies

Study	**Griffith et al., (2018)**	**McKinley, (2016)**	**Wawer et al, (2020)**
Were the two groups similar and recruited from the same population?	Yes	Yes	Yes
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
Were confounding factors identified?	Yes	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unsure	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Unsure	No	Yes
Were strategies to address incomplete follow up utilized?	Yes	No	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes

Appendix 4.

Quality Appraisal Results Using the Mixed Methods Appraisal Tool

Study	**Talisayon et al., (2011)**
Is there an adequate rationale for using a mixed methods design to address the research question?	Yes
Are the different components of the study effectively integrated to answer the research question?	Yes
Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	Yes
Are divergences between quantitative and qualitative results adequately addressed?	Yes
Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?	Yes

Appendix Digital Content 5.

Response Rates

Study	**Number of eligible patients contacted (n)**	**Number of participants in study (n)**	**Response rate (%)**
Asimakopoulou & Madianos, (2014)	150	102	68
Bohm et al., (2019)	491	442	90
Griffith et al., (2018)	240	165 (6 month) 155 (12 month)	64.5 (6 month) 68.75 (12 month)
McKinley, (2016)	344	193	56
Talisayon et al., (2011)	Not reported	97	Not reported
Wawer et al., (2020)	208	145	69.7