From the Department of Physiology and Pharmacology

Karolinska Institutet, Stockholm, Sweden

SEX AND GENDER ASPECTS ON INTENSIVE CARE

ACCESS, INTENSITY AND OUTCOME

Erik Zettersten

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Sex and Gender Aspects on Intensive Care
Access, Intensity and Outcome

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Erik Zettersten

Principal Supervisor:
Associate Professor Emma Larsson
Karolinska Institutet
Department of Physiology and Pharmacology
Division of Anesthesiology and Intensive care

Co-supervisors:
Associate Professor Max Bell
Karolinska Institutet
Department of Physiology and Pharmacology
Division of Anesthesiology and Intensive care

Ph.D. Gabriella Jäderling
Karolinska Institutet
Department of Physiology and Pharmacology
Division of Anesthesiology and Intensive care

Opponent:
Professor Mia von Euler
Örebro Universitet
Dean, Faculty of Medicine and Health
Department of Medical Sciences

Examination Board:
Associate Professor Peter Sackey
Karolinska Institutet
Department of Physiology and Pharmacology
Division of Anesthesiology and Intensive care

Associate Professor Helén Seeman-Lodding
Göteborgs Universitet
The Institute of Clinical Sciences
Division of Anesthesia and Intensive care

Associate Professor Anders Ternhag
Karolinska Institutet
Department of Medicine
Division of Infectious Diseases

To my boys, for keeping me on my toes. To my wife, for everything.

POPULAR SCIENCE SUMMARY OF THE THESIS

Background

The intensive care unit (ICU) is a highly specialized unit in the hospital, to which only the most severely ill patients are admitted. In general, patients admitted suffer from organ failure, for example of the lungs or kidneys, and without intensive care the chance of survival is sometimes very limited. Often the patients are unconscious, either because of brain damage or because they need to be under pharmacologically induced unconsciousness, to be able to tolerate the pain associated with the illness and the treatment. This is naturally very labor intensive, and typically a team of physicians, nurses, physiotherapists and assistant nurses only tend to two to three patients. Needless to say, intensive care is expensive. Hence, there is a limited number of intensive care beds available. It is therefore of uttermost importance that admission and discharge of patients to and from the ICU is performed in a correct manner. *All* and *only* those patients deemed to be in need of intensive care should be treated in the ICU. The decision on who should be granted access is based on a number of variables. Patient sex is not one of them. Therefore, the ICU patient population sex ratio - with male predominance - is unsettling. This thesis aims at investigating that discrepancy.

Methods and results

Study I is aimed at investigating if there are different thresholds for patients to be admitted to the intensive care unit depending on whether they are men or women. This was a survey study, where we asked physicians in Sweden if they would admit a patient to the ICU, yes or no. Two identical surveys were distributed, and responders were randomized to one of the two. The only difference between the surveys was the gender of the patient in each case. Hence, any differences in admittance between case x in survey one and two would be attributable to the gender of the patient. Using this method, we could not observe any difference in admittance caused by the gender of the patient.

Study II is based on the same method as in study I, but instead of eight cases we only included one case. This survey was endorsed and distributed by the European Society of Intensive Care Medicine. Therefore, responders came from 75 different countries. As in study I, we could not find any difference in admittance to the ICU caused by the gender of the patient.

Study III investigates if there are any differences in how long patients stay in the ICU and sex-related differences in survival after intensive care, depending on if the patient is a man or a woman. We used a dataset with almost 9,000 patients cared for in the Karolinska University Hospital ICU between 2006-2016. Aiming at comparing equally severely ill patients we used different severity of illness scores in our statistical models. We found no differences in survival between men and women, but men had a lower probability of being discharged from the intensive care unit.

In **Study IV** we explored if the treatment given to patients in the ICU differed depending on whether the patient was a man or a woman. Using the same patient dataset as in study III, we investigated differences in the use of for example mechanical ventilation, various ICU-typical medications and dialysis. We found that given equal level of illness, men received slightly more intensive care.

Study V explored long-term survival following intensive care after infection with SARS-CoV-2. We investigated all COVID-19 patients in Sweden cared for in an ICU between early March 2020 and late June 2020, looking at sex-differences in the treatment provided in the intensive care unit and 90-days mortality. We found that men with COVID-19 received more mechanical ventilation, stayed longer in the ICU and had a higher mortality at both 30- and 90-days.

Conclusion

We could not observe gender bias against women regarding admitting them to the ICU, furthermore we found no differences in mortality between men and women following intensive care in general. Men appear to have a slightly greater need of intensive care, which to some extent can be explained by different reactions to disease in men and women. Men need more intensive care and have a higher risk of dying following infection with SARS-CoV-2.

Populärvetenskaplig sammanfattning

Bakgrund

En intensivvårdsavdelning (IVA) är en högspecialiserad enhet på sjukhuset där endast de svårast sjuka patienterna är inlagda. I allmänhet har intensivvårdspatienter ett eller flera sviktande organ, till exempel lungor eller njurar, och utan intensivvård är chansen för överlevnad mycket begränsad. Ofta är patienterna medvetslösa, antingen på grund av hjärnskador eller för att de måste vara sövda till följd av smärtan och obehaget orsakade av själva sjukdomen, alternativt i syfte att kunna ge nödvändig behandling utan att patienten utsätts för smärta. Detta är naturligtvis mycket arbetskrävande, och vanligtvis har ett team av läkare, sjuksköterskor, sjukgymnaster och undersköterskor bara ansvar för två till tre patienter. Personaltätheten samt behovet av avancerad medicinsk-teknisk utrustning gör att intensivvård är dyrt. Därför finns det ett begränsat antal intensivvårdsplatser tillgängligt. Det är således av yttersta vikt att inläggning och utskrivning av patienter till och från IVA utförs på ett korrekt sätt. *Alla* och *endast* de patienter som bedöms behöva intensivvård ska behandlas på IVA. Beslut om vem som ska läggas in på IVA baseras på ett antal variabler. Patientens kön är inte en variabel som ska få påverka det beslutet. Den könsskillnad som noterats i IVA-populationen - där män utgör en större grupp än kvinnor - är därför otillfredsställande. Denna avhandling syftar till att undersöka den skillnaden.

Metod och resultat

Studie I syftade till att undersöka om tröskeln för patienter att bli inlagda på IVA är olika beroende på om patienten var en man eller en kvinna. Två identiska enkäter distribuerades till läkare i Sverige, som randomiserades till en av enkäterna. Enkäten bestod av flera patientfall med en avslutande fråga om respondenten ansåg att patienten behövde läggas in på IVA, ja eller nej. Den enda skillnaden mellan enkäterna var patientens kön i de olika fallen. Följaktligen skulle alla skillnader i inläggning mellan fall X i enkät ett och två bero på patientens kön. Med den här metoden kunde vi inte observera någon skillnad i inläggning som kunde hänvisas till patientens kön.

Studie II bygger på samma metod som i studie I, men istället för åtta fall inkluderade vi bara ett fall. Denna studie fick stöd av European Society of Intensive Care Medicine som bistod i konstruktion och distribution av enkäten, som således fick stor spridning och vi fick svar från läkare i 75 olika länder. I likhet med studie I kunde vi inte se någon skillnad i antal inläggningar på IVA som kunde hänvisas till om patienten var en man eller kvinna.

Studie III hade som mål att undersöka om det finns några skillnader i hur länge patienter vårdas på IVA och om det finns skillnader i överlevnad efter intensivvården, beroende på om patienten är en man eller en kvinna. Vi använde en databas med nästan 9000 patienter som vårdats på Karolinska Universitetssjukhusets IVA mellan 2006 och 2016. För att jämföra lika svårt sjuka patienter konstruerande vi olika statistiska modeller som tog hänsyn till de poängsystem som används inom intensivvård för att bedöma grad av sjuklighet hos patienten. Vi hittade inga skillnader i överlevnad mellan män och kvinnor, men vi fann att kvinnor har högre sannolikhet att bli utskrivna.

I **studie IV** undersökte vi om behandlingen som ges till patienter på IVA skiljer sig beroende på om patienten är en man eller en kvinna. Med hjälp av samma databas som vi använde i studie III undersökte vi skillnader i användningen av t.ex. mekanisk ventilation, olika IVA-typiska läkemedel och dialys. Vi fann att givet samma sjukdomsgrad får män något fler medicinska åtgärder under intensivvården.

Studie V utforskar 90-dagarsmortalitet samt skillnader i överlevnad mellan män och kvinnor som vårdats för COVID-19 på intensivvårdsavdelningar i Sverige. Vi undersökte alla patienter i Sverige som vårdades på IVA mellan början av mars 2020 och slutet av juni 2020 med diagnosen COVID-19. Vi undersökte också eventuella skillnader i behandling mellan män och kvinnor. Vi fann att män med COVID-19 fick mer mekanisk ventilation, stannade längre på IVA och hade högre risk att dö.

Slutsats

Vi kunde inte observera någon skillnad i läkares vilja att lägga in patienter på IVA beroende på om patienten var en man eller en kvinna. Vi fann heller inga skillnader i risken att dö efter intensivvård beroende på om patienten var en man eller en kvinna. Män verkar ha ett något större behov av intensivvård, vilket till viss del kan förklaras av att män och kvinnor reagerar olika på olika sjukdomar, beroende bland annat på olika hormonuppsättningar och olika genuppsättningar. Män behöver mer intensivvård och har högre risk att dö efter infektion med SARS-CoV-2.

ABSTRACT

There is an underlying assumption in society that critically ill patients are admitted to an intensive care unit (ICU) based on their illness severity coupled with their comorbidities, and that other variables are irrelevant. It is therefore troublesome to not fully understand the sex-discrepancy in the ICU-population; the gender distribution in intensive care units is consistently found to be around 60% men and 40% women. We sought to elucidate the reasons for this discrepancy by constructing five different studies, covering the entire chain from admittance to the ICU until 90 days post intensive care. The overall aim for this thesis is to investigate if there are differences in allocation of intensive care resources depending on whether the patient is a man or a woman.

The first two studies aimed at investigating gender differences in the afferent arm, i.e., the access to the ICU. This was done using surveys with fictive patient cases, where the respondent was to decide whether the patient in each case described was in need of ICU care or not. We concluded that in a blinded survey we could not see any differences in admittance to the ICU depending on whether the patient was a man or a woman.

Study III is a retrospective cohort study with 8,598 adult patients admitted between 2006 and 2016 to the ICU at Karolinska University Hospital in Stockholm, Sweden. This study explored differences in the efferent arm, i.e., sex- and gender-based differences in discharge from the ICU and mortality after intensive care. We found that women had a higher probability of being discharged from the ICU. There were no differences in 30- or 90-day mortality.

In Study IV we used the same cohort as in study III. In this retrospective cohort study, we explored care provided within the ICU, specifically different ICU-typical items, for example mechanical ventilation, vasoactive and inotropic treatment. We concluded that differences in the level of intensive care provided to men and women exist. Given equal severity of illness, men receive more intensive care.

Finally, in study V, we investigated differences between men and women regarding care provided in the ICU as well as long-term outcome for all ICU-treated patients with COVID-19 during the spring of 2020 in Sweden. Male sex was significantly associated with mortality. Additionally, age, COPD/asthma, immune deficiency, malignancy, SAPS 3 and admission month were associated with mortality. In this nationwide study of ICU patients with COVID-19 we concluded that men were at higher risk of poor long-term outcome compared to women.

LIST OF SCIENTIFIC PAPERS

I. **The influence of gender on ICU admittance**
Larsson E, Zettersten E, Jäderling G, Ohlsson A, Bell M
Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2015) 23:108

II. **The impact of patient sex on intensive care unit admission: a blinded randomized survey**
Zettersten E, Jäderling G, Larsson E, Bell M
Scientific Reports (2019) 9:14222

III. **Sex and gender aspects on intensive care. A cohort study**
Zettersten E, Jäderling G, Bell M, Larsson E
Journal of Critical Care 55 (2020) 22-27

IV. **The impact of sex on the intensity of intensive care. A cohort study**
Zettersten E, Jäderling G, Bell M, Larsson E
In manuscript.

V. **Long-term outcome after intensive care for COVID-19 infection – differences between men and women. A nationwide cohort study**
Zettersten E, Engerström L, Bell M, Jäderling G, Mårtensson J, Block L, Larsson E
Critical Care 2021 Feb 25;25(1):86.

CONTENTS

LIST OF ABBREVIATIONS

ICU	Intensive Care Unit
NOS	Not Otherwise Specified
COVID-19	Corona Virus Disease 2019
AMI	Acute Myocardial Infarction
DNR	Do Not Resuscitate
IAT	Implicit Association Test
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
ICU-LOS	Intensive Care Unit Length of Stay
ICD-10	International Statistical Classification of Disease and Health Related problems – Tenth Revision
APACHE II	Acute Physiology and Chronic Health Evaluation II
SAPS 3	Simplified Acute Physiology Score 3
SIR	Svenska Intensivvårdsregistret (Swedish Intensive Care Registry)
ESICM	European Society of Intensive Care Medicine
GEE	General Estimation Equation
SOFA	Sequential Organ Failure Assessment
KARDA	Karolinska Universitetssjukhusets Datalager (Karolinska University Hospital Database)
CCI	Charlson Comorbidity Index
EMR	Estimated Mortality Risk
SHR	Sub-distribution Hazard Ratios
CI	Confidence Interval
IQR	Interquartile Range
OR	Odds Ratio
BMI	Body Mass Index

COPD	Chronic Obstructive Pulmonary Disease
HR	Hazard Ratio
RRT	Renal Replacement Therapy

1 INTRODUCTION

When suffering from a disease that requires hospital care, patients are generally admitted to a hospital ward. If the disease causes organ failure that progresses beyond the capabilities of the ward, the patient needs to move to a unit with more resources. The highest level of care is in the intensive care unit (ICU). An ICU can offer the patient advanced monitoring and organ support, with a high level of staffing around the clock. But intensive care is expensive, and ICU beds are few and far between. This leads to a situation where there is a shortage of ICU beds. Hence some sort of selection needs to take place in order to secure that the patient in most need of intensive care is the patient who gets access to intensive care, but also that no patient in need is left without.

More women than men are admitted to hospital in Sweden, but more men are admitted to the ICU (1). The assumption is naturally that this is in concordance with ethical values dictated by Swedish law; The principle of human dignity – according to which all people have equal value and the same right regardless of personal characteristics and social status; Needs and solidarity principle – according to which resources should be invested in areas (individuals or activities) where the needs are greatest; Cost-effectiveness principle – according to which a reasonable relationship between costs and impact, measured in terms of health and quality of life, should be sought when choosing between different measures or activities (2,3). Recognizing the above mentioned discrepancy between men and women in the ICU population as medically sound without reservations is problematic, in view of the fact that previous research in other medical fields have suggested otherwise (4–12). Likewise, prior research on sex and gender differences in ICUs have indicated that men receive more intensive care and have a longer length of stay (13–16), but results are conflicting, in particular concerning differences in mortality (17–21). Notwithstanding, if the assumption holds true and the discrepancy between men and women in the ICU is motivated by sound medical and ethical decisions, it is of interest to unveil the underlying reasons. It could denote a sex or gender driven general increased risk for men to develop severe illness.

The aim of this thesis in short is to elucidate if differences in admittance, intensity of and outcome from intensive care differ between women and men. Both social and biological effects of gender and sex will be studied. In the first part of the thesis, we investigated if there were any differences in accessibility to an intensive care unit, using blinded randomized surveys. For the second part, we investigated differences in the probability of being discharged from an intensive care unit and if there were any differences between women and men regarding the level of intensive care provided once admitted. These questions were approached using data from the intensive care unit at Karolinska University Hospital Solna. Finally, we studied differences between women and men in outcome after severe COVID-19 infection, using the Swedish Intensive Care Unit register, accessing all ICU COVID-19 patients in Sweden between March 2020 and October 2020.

2 BACKGROUND

2.1 EPIDEMIOLOGY

Intensive care is for patients with acute, life-threatening conditions who are in need of continuous surveillance and possible interventions to sustain organ function. This care is often provided in an intensive care unit but can also be given in an emergency room and during transport of a critically ill patient (22). According to the Swedish Intensive Care Registry, there are around 45,500 admissions per year to Swedish ICUs. In 2020, there were 43,971 admissions. The coronavirus pandemic renders 2020 and 2021 to be exceptional and not comparable to other years. In Sweden, there were fewer ICU admissions in total compared to 2019 (23). This might be caused by an increased length of stay in ICU for patients with Corona virus disease-19 (COVID-19) (24,25) compared to other diagnoses (13). It also appeared as if there were fewer admissions to ICU for other reasons then COVID-19, possibly caused by the need for postponing elective surgery and the general effect of a society in pandemic lockdown. In 2019 there were 45,478 admissions, the five most common diagnoses were interstitial pulmonary disease (NOS), trauma, bacterial infection, pneumonia and intoxication. There were more men (59.2%) than women and the median age in years was 58.6 and 59.7 for women and men respectively. 30-day mortality at a nationwide level was 15.7% for men and 16.0% for women. Corresponding 90-day mortality for men was 19.2% and 18.8% for women (23). 1,265,033 patients were admitted to hospital in 2019. Of them, 686,255 (54.2%) were women (26).

2.2 DEFINITIONS OF GENDER AND SEX

Gender and sex are often used interchangeably. This is not in line with current discourse, and when it is used interchangeably it is somewhat difficult to interpret if research has been done with regard to sex or gender. It is likely that this issue is frequently overlooked, i.e., that sex and gender are used as synonyms, when they in fact have two different meanings.

2.2.1 Gender

The World Health Organization defines gender as the socially constructed roles, behaviors, activities and attributes that a given society considers appropriate for men and women. Gender identity is one´s innermost concept of being male, female, a blend of both or neither (27).

2.2.2 Sex

Sex is broadly defined as either of the two main categories (male and female) into which humans and most other living species are divided on the basis of their reproductive functions. Specifically, a person is typically categorized as being male if they carry chromosomes X and Y, or female if they carry X and X. However, it has been reported that roughly 1.7% of humans are intersex (28). When conducting this research, we only had access to the patients’ legal sex, i.e., the sex registered in the social security number. Therefore, we dichotomize male/female based on the patients' social security number.

2.3 GENDER DISPARITY IN HEALTH CARE

The field is vast and heterogeneous, and it is somewhat difficult to interpret if previous research has been done with regard to sex or gender, i.e., is the research question one for biological differences or social? Regardless, there is a vast body of evidence from different fields within health care that all point in the same direction; for some unclear reason men and women are treated in different ways. For example, women are less likely to get guideline treatment when suffering acute myocardial infarction (AMI) (29–32), both in the acute period but also with regard to secondary prevention. Furthermore, it is reported that women are less likely to receive evidence-based treatment for congestive heart failure (11,33), experience more emergency department delays (34) and receive less evidence-based treatment when presenting with stroke (35). These findings are not restricted to conditions with acute illness progression, like stroke and AMI. For some reason it appears that women received less information and encouragement than men when being referred for total knee arthroplasty (36) and there is a threefold underuse of arthroplasty in severe arthritis among women compared to men (12). Women are more prone to develop chronic kidney disease (37), but men are more often on haemodialysis and are more often recipients of kidney transplants (12). In summary, evidence suggests that there is a discrepancy in the level of care given to men and women. However, registry-based studies are always associated with certain limitations and results must be interpreted with that in mind.

2.4 GENDER DISPARITY IN INTENSIVE CARE

It is fair to say that the intensive care patient cohort is very heterogeneous, from young to old, with a wide range of comorbidities and different medical or surgical disorders leading to acute organ failure and need of support, especially at a mixed ICU. All of this makes it difficult to investigate and compare treatment between men and women with the only common denominator being that they are treated at an ICU. It is therefore understandable that there are only a handful of studies with the object of understanding how the biological sex of the patient affects access to, treatment within and survival after intensive care. That being said, certain specific diagnoses, for example sepsis and differences in treatment and survival within the ICU has previously been studied (38–41). In conformity with the sex/gender-oriented research questions discussed above, it is not always clear whether biological sex or gender has been the focus of the research and despite being distinctive entities sex and gender are often used indistinctively, which also complicates interpretation of previous research. It can nonetheless be concluded that women are far fewer in the ICU population (13–16). Furthermore it has been reported that women have a shorter length of stay (13,16,17) undergo less invasive procedures (15) and are less likely to receive mechanical ventilation (14,17). As previously addressed, this conundrum has yet to be solved.

It is not clear whether reported differences in treatment between men and women in the ICU translates into any difference in mortality. The majority of studies report no difference in mortality (15,17–19) but there are reports of an increased mortality for women (14,20,21) as well as increased mortality for men (16). In an extensive study from the Apache IV registry, with more than 260,000 patients, women under 50 years of age had a lower mortality, while there was no difference in mortality between men and women over 50 years (13). Concerning differences in mortality after intensive care and sepsis, data is conflicting. In an early study, Eachempati et al found women to have a higher mortality than men in a cohort of surgical ICU patients with documented infection (29). Similar results were found in a large study of over 18,000 patients with severe sepsis, where women had a higher hospital mortality in all age groups, including women over 50 years of age, which is the median age of menopause in the USA (31). However, in smaller studies, women had a lower mortality (38,40,42) which makes any conclusions regarding sex-based differences in mortality more difficult. Similar difficulties arise when studying other critical illnesses. Shoenberg et al investigated if there were any differences in mortality in a cohort of severely ill trauma patients and conclude that women are more likely to die in the first days, but men have a higher mortality risk if the hospital stay is prolonged. They further conclude that women in their cohort have a lower risk of sepsis, which may drive survival rates towards being more favorable for women (43). Brattström et al reported similar results. They found men to have a higher 360-day mortality after trauma compared to women (44). The most in-depth analysis of mortality after trauma is presented in a relatively recent meta-analysis, where women appeared to have a lower risk of mortality in all groups except in that of the most injured patients (45).

In the final stages of life or when further intensive care is deemed futile, a do-not-resuscitate (DNR) order is often written. It has been found that for patients who underwent emergency surgery women had a higher risk of receiving a do-not-resuscitate order (46). Furthermore, physicians were more prone to order a DNR on a woman who sustained an intracerebral haemorrhage than on a man with similar injury (47). Contesting this is a study from Lissauer et al. When investigating post-operative care, they found that men had a three times higher probability of receiving a DNR (48).

In conclusion, opinions regarding sex- and gender-based differences in intensive care and mortality are divergent and the true nature of any such differences is yet to be revealed.

2.5 GENDER BIAS

Differences in treatment or outcome between patients of opposite sex that cannot be otherwise explained could be caused by gender bias. It is unlikely that explicit gender bias exists in health care at a group level (49) but there might still be implicit bias. Implicit bias is attitudes and beliefs about a person or a group that is held on an unconscious level, or when someone acts in a prejudiced way, whilst not intending to do so. This behavior can be automatic and unintentional, and the person acting in a prejudiced way can be unconscious of the fact that their behavior could be perceived as prejudiced. Early work by Fazio et al indicated that attitudes can be activated either by controlled or automatic processes, and when attitudes were automatically activated, they were more prone to be prejudiced. Other studies revealed that awareness of stereotypes could affect social behavior in relative independence from subjects´ reported attitudes (50). Devine demonstrated that white students who had a low-prejudice attitude towards black persons would stereotype a black person in the same way as a white student with high-prejudice towards black people. In the next stage of research, it was shown that if restrained from cognitive reflection, i.e., when acting on instinct, the low-prejudice group would act in a similar way as the high-prejudice group (51). Hence, just knowing about a stereotype increases the risk of acting in a prejudiced way, if not given the opportunity to correct the behavior. Explicit bias is beliefs and attitudes (positive or negative) about a person or a group on a conscious level.

There are several ways to test implicit bias, but the most widely used test is the Implicit Association Test (IAT). The test builds on reaction time measurement, were the test subject sort words or pictures into categories as fast as possible, whilst making as few errors as possible. The subject will be faster and make fewer errors when sorting words that are more congruent with the test subject´s beliefs. The attitudes become implicit if the test subject denies having those attitudes in the first place (50).

2.6 COVID-19

When nearing the end of working with this thesis, the world saw the dawn of a new strain of coronavirus emerging from Wuhan, China. Scarce reports concerning a deadly viral pneumonia started coming out of China in December 2019, and by mid-January 2020 China reported its official first casualty (52,53). By the end of January 2020, the virus had spread to 18 countries outside China. Italy was one of the first countries in Europe where the virus, now known as Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), gained a strong foothold and the rest of Europe held its breath as reports about the chaotic situation in Italy in general, and hospitals in particular, were presented in the news. The virus had spread to Sweden in February 2020 and the first patient in need of intensive care because of Coronavirus disease-19 (COVID-19) was admitted to an ICU on March 6, 2020. Early epidemiological work from China and Italy (54,55) suggested that men where at higher risk for developing severe respiratory disease, which was clinically observed in Swedish ICUs. For obvious reasons, considering the novelty of the disease, no long-term outcome data was available. Since all citizens in Sweden have a unique personal identification number, which is needed in all contact with healthcare and authorities, patients are very seldom lost to follow-up. We were therefore in the unique position of being able to add knowledge concerning long-term outcome to the research field. We thus aimed at investigating differences in long-term mortality between men and women with COVID-19 treated in Swedish ICUs. We also aimed at investigating differences between men and women regarding treatment in the ICU.

3 AIMS OF THESIS

To test if the threshold for being admitted to intensive care differs if the patient is a man or a woman.

To study if physicians make different choices in admitting patients to ICU, based on the physician´s gender or specialty.

To investigate if patient sex affects ICU-LOS, probability of discharge and 30- and 90-day mortality.

To investigate differences in admission characteristics in the form of comorbidities and severity of illness between men and women.

To investigate any differences between men and women regarding the intensity of intensive care provided within the ICU.

To analyze long-term outcome beyond 90 days in critically ill patients with COVID-19, with special focus on differences between men and women.

4 MATERIALS AND METHODS

4.1 OVERVIEW

	Study I	Study II	Study III	Study IV	Study V
Short title	The influence of gender on ICU admittance	The impact of patient sex on intensive care unit admission	Sex and gender aspects on intensive care	The impact of patient sex and gender on the intensity of intensive care	Long-term outcome after intensive care for COVID-19
Design	Randomized survey study	Randomized survey study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Study Participants	1,426 Swedish physicians	1,004 physicians and nurses associated with ESICM	8,598 ICU patients admitted between 2006-2016	9,067 ICU patients admitted between 2006-2016	2,354 COVID-19 ICU patients in Sweden
Main outcome	If threshold for admitting male or female patients differ	If threshold for admitting male or female patients differ	Sex-related difference in ICU length of stay and probability of being discharged	Sex-related difference in intensity of intensive care	Sex-related difference in 90-day mortality
Secondary outcome	If physician sex and field of specialty has an impact on admission rates	If respondents sex has an impact on admission rates.	Sex-related difference in 30- and 90-day mortality		Sex-related differences in baseline comorbidities and processes of care
Statistical method	Pearson´s chi-square test	Pearson´s chi-square and GEE	Wilcoxon rank-sum test, Pearson´s chi-square test, Fine-Gray competing risk regression model and a quantile regression model	Wilcoxon rank-sum test, Pearson´s chi-square test and a logistic regression model	Kaplan-Meier with a log-rank test, Cox-regression model and a logistic regression model

ICU Intensive care unit; *ESICM* European Society of Intensive Care Medicine; *GEE* Generalized estimation equation

4.2 ETHICAL CONSIDERATIONS

Studies I-IV were approved by the Regional Ethics Review board in Stockholm (approval number 2017/1074-32 and 2014/756-31/1). Study V was approved the Swedish Ethical Review Authority (approval number 2020-01477). For studies I and II responders were acknowledged as test subjects. They were informed about the general aim of the study prior to agreeing to participate. Studies III-V are retrospective register studies, and as such written consent was waived. Nevertheless, the data are considered as highly sensitive under law, as stated by the Swedish Authority for Privacy Protection. Data has therefore been handled and reported in such a way that the risk of identifying a patient is minimal.

4.3 REGISTERS AND DATABASES

4.3.1 PDMS, Clinisoft®

Clinisoft is the electronic ICU patient data management system used at Karolinska University Hospital during the study period. All patients admitted to ICU are connected to Clinisoft, regardless of whether the patient is identified or has temporary patient number. Data on admission time and discharge time and use of different ICU items are manually registered by ICU nurses. International Statistical Classification of Disease and Related Health Problems – Tenth Revision (ICD-10) codes, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score 3 (SAPS 3) are manually entered by a physician. Data is then validated, and if needed corrected by a designated Clinisoft administrator.

4.3.2 Karolinska Database

The Karolinska Database is an inhouse database at Karolinska University Hospital that contains patient data from different sources; the electronic medical record, the surgical planning system, Karolinska University Laboratory, the Radiology Information System and several quality registries, for example Swedeheart and Swedish Rheumatology Quality Register.

4.3.3 The Swedish Intensive Care Registry

The Swedish Intensive Care Registry (SIR) collects individual patient data from all intensive care units in Sweden, within the legal framework of the Swedish National Quality Registries (56). Data in SIR includes demographics, comorbidities, treatment given within the ICU and variables included in SAPS 3. Data is transferred electronically to SIR after local validation at each hospital. After validation at SIR, any incomplete or inconsistent patient records are returned to the source for correction before accepted and added to the master database.

4.4 STUDY I

4.4.1 Design and study population

A survey of eight patient cases was distributed to physicians working in any of the 15 largest hospitals in Sweden. Only physicians working in fields that come in contact with intensive care units, e.g., surgeons, anesthesiologists and emergency physicians were approached. The responders were randomized to one of two identical surveys, bar the sex of the patient (case one in survey A portrayed a woman, and the identical case one in survey B portrayed a man, and so on). The cases described real intensive care events but were tweaked in a way so that it would be debatable if the patient should be admitted to an ICU. At the end of each case, the respondent was asked if they would admit the patient to an ICU, yes or no. Any differences in admittance between each case in survey A and B would in theory be attributable only to the sex of the patient. Responders were randomized based on their date of birth. 1426 physicians responded to the survey, which represented approximately a 30% response rate.

4.4.2 Statistical analysis

We compared differences in admittance rate depending on whether the patient was a woman or a man. Furthermore, we investigated if there were any differences in admittance to ICU depending on if the physician was a woman or a man, regardless the of sex of the patient. Finally, we compared differences in admittance rate between anesthesiologists/intensive care physicians and all other specialties combined, regardless the sex of the patient. Differences in proportions were compared using Chi-squared test. All tests were two-sided and a p-value of <0.05 was considered as statistically significant.

4.5 STUDY II

4.5.1 Design and study population

The design is analogous to the design in study I but using only one patient case, choosing the case in study I that proved most contentious. The study was endorsed by the European Society of Intensive Care Medicine (ESICM) and the survey was accessible via a hyperlink on ESICMs webpage. The survey was promoted via ESICMs newsletter and social media channels. Responders were randomized to either critical case Jane or critical case John, utilizing a randomization function in the software used for designing the survey (Surveymonkey, SurveyMonkey INC, San Mateo, USA). 1,004 individuals from 75 different countries replied to the survey.

4.5.2 Statistical analysis

Differences in admittance rate between Jane/John and differences in admittance rate depending on if the responder was a man or a woman, regardless the sex of the patient, was analyzed. Differences in proportions were compared using Chi-squared test. All tests were two-sided. A p-value <0.05 was considered statistically significant. A Generalized Estimating Equation (GEE), clustering on country, was used to investigate if the respondent's country of residence had an impact on willingness to admit patients to the ICU.

4.6 STUDY III

4.6.1 Design and study population

In this retrospective cohort study, we aimed at investigating differences between men and women in ICU length of stay, probability of discharge and 30- and 90-day mortality in a cohort of patients from a mixed ICU at Karolinska University Hospital between January 2006 to December 2016. Cardiothoracic, neurological and pediatric patients are treated in separate ICUs. All first-admission ICU patients ≥18 years old were eligible for inclusion. After excluding patients not found in the Karolinska Database (KARDA) and readmitted patients, 8,598 patients were included. The analysis was performed on the entire cohort and on the non-trauma cohort separately, since the trauma cohort is distinctively different in age, sex and comorbidities. Data was extracted from the electronic ICU patient data management system (PDMS, Clinisoft®, GE Healthcare) and included age, sex, comorbidities, admission diagnosis codes, SOFA, APACHE II, SAPS 3, time for admission and discharge. Data on length of stay in hospital prior to ICU and mortality was extracted from KARDA.

4.6.2 Statistical analysis

Comparison of categorical variables was performed using Pearson´s chi-squared test. Continuous variables were compared using Wilcoxon rank-sum test and presented as median and interquartile range. Differences in length of stay in wards and emergency rooms prior to ICU admittance was analyzed using a quantile regression model. Statistical analysis was performed on the entire cohort and after excluding trauma patients. Differences between men and women in median length of stay in the ICU were analyzed using the same method. A priori selected variables including age, probability of mortality and Charlson Comorbidity Index (CCI) were included in a multivariable quantile regression model. Results are presented as median differences (β) and corresponding 95% confidence interval (CI).

When comparing length of stay it is important to consider death as a competing risk of being discharged. For that reason, we also performed a Fine-Gray competing risk regression model, treating death in the ICU as a competing event. We divided the cohort into a trauma and non-trauma group. A priori selected variables included age, probability of mortality, CCI and SOFA score for the day of discharge. Results are presented as sub-distribution hazard ratios (SHRs) with corresponding 95% CI.

4.7 STUDY IV

4.7.1 Design and study population

The aim of study IV was to investigate if the care provided within the ICU differed depending on if the patient was a man or a woman. We approached this question using the same cohort as in study III. Through the ICU patient data management system (PDMS, Clinisoft®, GE Healthcare), we had access to the care provided within the ICU. We decided a priori to specifically investigate differences in treatment in the form of invasive ventilation, use of vasoactive drugs, inotropic drugs, renal replacement therapy, invasive monitoring, evaluation with echocardiography and placement of central venous catheters between men and women. We were interested in investigating differences in the entire cohort, but foremost in patients admitted with a primary diagnosis of respiratory origin, sepsis or post cardiac arrest. Subgroup analysis was therefore performed on these diagnoses.

4.7.2 Statistical analysis

Continuous variables were compared using Wilcoxon rank-sum test and presented as median and interquartile range (IQR). Comparison of categorical variables was performed using Pearson´s chi-squared test. Comparison between the aforementioned intensive care items between men and women was done using a logistic regression model, both for the entire cohort as well as the subgroup analysis. Variables in the multivariable model were selected a priori and included age, estimated mortality risk and CCI. Results are presented as odds-ratios (ORs) and corresponding 95% CI.

4.8 STUDY V

4.8.1 Design and study population

This retrospective cohort study aimed at investigating long-term outcome beyond 90-days in a cohort of patients with COVID-19 treated in ICUs in Sweden. The first patient was admitted to a Swedish ICU on March 6, 2020. Long-term mortality was for obvious reasons not known at this point. We set out to investigate outcome beyond 90 days, with special focus on differences between men and women. We performed a nationwide retrospective cohort study, extracting data from the Swedish Intensive Care Registry on all COVID-19 patients cared for in an intensive care unit in Sweden between March 6 and June 30, 2020. Patients were then followed until death or study endpoint, which was October 30, 2020.

4.8.2 Statistical analysis

Categorical variables were presented as number with percentage. Continuous variables were presented as median and interquartile range (IQR). Kaplan-Meier estimator with a log-rank test was used to evaluate differences in time to death.

Patient sex, age, comorbidities (cardiac disease, chronic obstructive pulmonary disease (COPD)/asthma, morbid obesity (BMI>40kg/m^2), hypertension, immune deficiency, chronic liver disease, chronic kidney disease, neuromuscular disease and malignancy (neoplasia spread beyond regional lymph nodes)), hospital level (local, county or tertiary) and admission month (March, April, May or June) and its association with mortality were estimated using univariate and multivariable Cox regression models and expressed as hazard ratios (HRs) with corresponding 95% CI. We also constructed a similar logistic regression model, estimating factors associated with 90-day mortality. Results were expressed as odds ratios (ORs) with corresponding 95% CI.

5 RESULTS

5.1 STUDY I

The survey had 1,426 respondents. After contact with human resources departments at the different hospitals, we approximated the number of possible responders to 4,800. This would render us a response rate of 30%. The majority of respondents were between 30-39 years of age. Baseline demographic data of respondents are provided in table 1. We found no significant differences in admittance rate based on the gender of the patient (table 2). Women physicians tended to be more willing to admit patients, regardless of the gender of the patient (table 3). Compared to all other specialties, anesthesiologists/intensive care physicians were more willing to admit patients in five out of eight cases.

Table 1. Demographic data of respondents

	Survey 1 n = 679	Survey 2 n = 747
Gender (n, %)		
Women	298 (43.9 %)	320 (42.8 %)
Men	381 (56.1 %)	427 (57.2 %)
Age (years, %)		
20–29	31 (4.6 %)	23 (3.1 %)
30–39	279 (41.1 %)	288 (38.6 %)
40–49	188 (27.7 %)	229 (30.7 %)
50–59	108 (15.9 %)	126 (16.9 %)
60–69	71 (10.5 %)	78 (10.4 %)
70-79	2 (0.3 %)	3 (0.4 %)
Type of Hospital (n, %)		
Regional Hospital		542 (72.6 %)
Central Hospital	151 (22.2 %)	173 (23.2 %)
Rural Hospital	22 (3.2 %)	21 (2.8 %)
Not given	11 (1.6 %)	11 (1.5 %)
Title (n,%)		
Resident	236 (34.8 %)	247 (33.1 %)
Board certified specialist	148 (21.8 %)	174 (23.3 %)

	Survey 1 n = 679	Survey 2 n = 747
Assistant senior physician	37 (5.4 %)	39 (5.2 %)
Senior Physician	258 (38.0 %)	287 (38.4 %)
Specialty (n,%)		
Emergency medicine	30 (4.4 %)	32 (4.3 %)
Anesthesiology /Intensive Care	166 (24.4 %)	166 (22.2 %)
Gynecology	52 (7.7 %)	47 (6.3 %)
Infectious diseases	44 (6.5 %)	64 (8.6 %)
Cardiology	44 (6.5 %)	46 (6.2 %)
General surgery	80 (11.8 %)	80 (10.7 %)
Internal medicine	125 (18.4 %)	135 (18.1 %)
Oncology	39 (5.7 %)	47 (6.3 %)
Orthopedic surgery	54 (8.0 %)	71 (9.5 %)
Urology	15 (2.2 %)	21 (2.8 %)
Ear, Nose, Throat	27 (4.0 %)	33 (4.4 %)
Other	3 (0.4 %)	4 (0.5 %)

Table 2. Female vs. male gender of the patient

	Female patient	Male patient	p-value
Case 1	39.9 %	39.0 %	n.s.
Case 2	37.9 %	38.3 %	n.s.
Case 3	40.4 %	43.9 %	n.s.
Case 4	70.7 %	68.1 %	n.s.
Case 5	63.0 %	62.0 %	n.s.
Case 6	66.9 %	69.8 %	n.s.
Case 7	48.9 %	53.3 %	n.s.
Case 8	65.6 %	63.6 %	n.s.

Proportion of patients deemed in need of ICU care dependent of patient gender

Table 3. Respondent: female vs. male, regardless of the gender of the patient

	Female respondent	Male respondent	p-value
Case 1	42.4 %	37.0 %	0.04
Case 2	37.1 %	38.9 %	n.s
Case 3	41.4 %	42.8 %	n.s.
Case 4	72.0 %	67.3 %	n.s.
Case 5	67.5 %	58.7 %	0.001
Case 6	73.5 %	64.4 %	<0.001
Case 7	47.4 %	54.1 %	0.01
Case 8	62.8 %	66.1 %	n.s.

5.2 STUDY II

The survey received 1,004 responders from 75 different countries (table 4). There was no significant difference in admitting female patient “Jane” or male patient “John” to an ICU (Jane 68.3% vs. John 70.1%, p=0.341) (table 5), nor was there a difference in admittance depending on the gender of the respondent. This was further established after having performed a GEE clustering on country.

Table 4. Demographics of the respondents

Responders	Jane case	John case
Gender (n, %)		
Female	158 (32.9)	162 (32.2)
Male	323 (67.1)	341 (67.8)
Age (n, %)		
21–30	36 (7.5)	45 (9.0)
31–40	198 (41.2)	203 (40.7)
>41	247 (51.4)	251 (50.3)
Type of hospital (n, %)		
Urban	86 (17.9)	100 (20.0)
Regional	115 (23.8)	114 (22.8)
University Affiliated	282 (58.4)	287 (57.3)
Specialty (n, %)		
Anaesthesiology	276 (57.0)	298 (59.2)
Critical/Intensive Care Medicine	93 (18.4)	99 (20.4)
Cardiology	9 (1.9)	5 (1.0)
Internal medicine	55 (11.4)	59 (11.7)
Surgery	6 (1.2)	4 (0.8)
Other	45 (0.9)	38 (0.8)

Table 5. Female vs. male responder, regardless the gender of the patient. *Chi-square test.

Gender of Respondent	Admitting patient (n, %)	
	No	Yes
Female	97 (30.3)	223 (69.7)
Male	198 (29.7)	465 (70.1)
		p* = 0.886

5.3 STUDY III

Of the 8,598 included patients with a primary ICU admission, 36.6% were women. After excluding trauma patients men were older, had a higher CCI and higher median SAPS 3 and probability of mortality than women. There was no difference in median APACHE II.

In the univariate analysis, median LOS in hospital prior to ICU admission was significantly longer for women with a median time of 3.7 hours vs 2.4 hours for men ($\beta = {}^{-}1.3$ hours, (95% CI ${}^{-}1.77$-${}^{-}0.86$)). In the multivariable analysis the difference was no longer significant. After excluding trauma patients similar results were noted. No differences were noted in the multivariable models when analyzing non-trauma patients admitted from the emergency department and hospital wards separately.

Median ICU-LOS for women was 34.1 hours and for men 37.4 hours. After adjustment in the multivariable quantile regression model there was no detectable difference between men and women. After excluding trauma patients median ICU-LOS for women and men were 35.7 hours and 40.6 hours respectively. This discrepancy proved non-significant in the multivariable analysis (table 3).

In the competing risk analysis after adjustment for age, CCI, probability of mortality and SOFA score, men had a lower probability at any time of being discharged from the ICU compared to women (SHR 0.94, 95% CI 0.90-0.99) (table 6). Analysis without SOFA score did not change the results. When stratifying on trauma and non-trauma patients there was no evidence of a sex difference in probability of being discharged.

30-day mortality was 14.4% for women and 13.5% for men. Corresponding results for non-trauma patients was 15.2% and 18.0%. 90-day mortality was 18.5% for women and 17.5% for men. 90-day mortality for non-trauma patients was 20.5% for women and 23.3% for men. In the logistic regression model, there was no evidence of a sex difference in 30- or 90-day mortality in the non-trauma group or when including all patients. Analysis without SOFA as an explanatory variable did not change the results (table 7).

Table 6. Univariate and multivariable Fine-Gray competing risk regression model exploring probability of being discharged from the ICU, data presented as Sub-distributed Hazard Ratio (SHR) and 95% CI.

Patients	Univariate	Multivariable[d]
All patients[a]		
Female	Ref	Ref
Male	0.97 (95% CI 0.92–1.01)	0.94 (95% CI 0.90–0.99)
Trauma patients[b]		
Female	Ref	Ref
Male	1.03 (95% CI 0.93–1.14)	0.94 (95% CI 0.84–1.04)
Non-trauma patients[c]		
Female	Ref	Ref
Male	0.92 (95% CI 0.87–0.97)	0.95 (95% CI 0.90–1.00)

[a]8598 and 8394 patients included in univariate and multivariable analyses respectively.
[b]2346 and 2265 patients included in univariate and multivariable analyses respectively.
[c]6252 and 6129 patients included in univariate and multivariable analyses respectively.
[d]Adjusted for age, probability of mortality and CCI.

Table 7. Univariate and multivariable logistic regression analyses exploring 90-day mortality, data presented as OR (95% CI).

	Univariate	Multivariable[c]
All patients[a]	Ref	Ref
Female		
Male	0.9 (0.8–1.0)	1.0 (0.8–1.1)
Non-trauma[b]	Ref	Ref
Female		
Male	1.2 (1.0–1.3)	1.0 (0.9–1.2)

[a]8658 and 8394 patients included in univariate and multivariable analyses respectively.
[b] 6270 and 6129 patients included in univariate and multivariable analyses respectively.
[c]Adjusted for age, probability of mortality, CCI and SOFA score on day of discharge.

5.4 STUDY IV

In total 9,067 patients were included in the study. There were more men than women admitted to the ICU, with a male dominance of 63.6%. Median [IQR] age (61 [41 – 72] vs. 59 [41 – 70]; p = 0.001) and estimated mortality risk (11.1 [3.1 – 29.9] vs. 9.9 [2.9 – 29.1]; p = 0.03) were statistically higher in women. According to admission diagnosis, women were more likely to be admitted with a respiratory disease (22.6% of the women vs. 18.2% of the men; p < 0.001), neurological disease (2.2% vs. 1.4%; p = 0.01), intoxication (5.5% vs. 4.4%; p = 0.018), sepsis (12.7% vs. 10.2%; p = 0.004) or other (7.4% vs. 5.5%; p = 0.000) whilst men were more likely trauma patients (30.0% of the men vs. 15.9% of the women; p = 0.000).

Overall, men were more likely to receive mechanical ventilation (OR 1.28 (95% CI 1.17 – 1.41)), vasoactive treatment (OR 1.16 (95% CI 1.06 – 1.27)) and intermittent haemodialysis or continuous renal replacement therapy (RRT) (OR 1.21 (95% CI 1.04 – 1.40)) (table 2). In additional subgroup analyses, men were more likely to be administered levosimendan if admitted to ICU with sepsis (OR 1.45 (95% CI 1.03 – 2.04)) or cardiac arrest (OR 2.11 (95% CI 1.27 – 3.49)). If admitted with a cardiac arrest diagnosis, men more often received a central venous line (1.60 (95% CI 1.04 – 2.45)) (table 3 and 4). Men were also more likely to receive mechanical ventilation (1.22 (95% CI 1.01 – 1.49)) if admitted with a respiratory diagnosis (table 5). Women were not more likely to receive any of the items investigated.

5.5 STUDY V

During the study period, 2,481 ICU patients with confirmed SARS-CoV-2 were reported to SIR. We excluded 127 patients who were admitted to ICU with a primary diagnosis not associated with COVID-19 (n=64), had a temporary Swedish personal identification number (n=62) or invalid registration data (n=1). In total, 2,354 patients with laboratory-confirmed COVID-19 were included in the final analyses. 73.2% were men. Median age was 61 (IQR 52-69) years for the entire patient cohort, 60 (IQR 50-70) and 61 (IQR 53-69) years for women and men respectively. Median duration of symptoms before ICU admission was 10 (IQR 7-13) days. Of the 632 women included in the study, 20 (3.2%) were pregnant at ICU admission. 851 (36.2%) patients had no reported comorbidity at admission; no comorbidities were noted in 216 (34.2%) women and 635 (36.9%) men respectively. 74.7% received invasive mechanical ventilation for a median total duration of 313 (IQR 186-534) hours. Corresponding figures for women were 70.3% with a duration of 266 (IQR 165-443) hours and for men 76.3% with a duration of 331 (191-571) hours. Renal replacement therapy and prone position was reported in 19.2% and 46.3% of the patients respectively, both treatments were more common in men than women. Median total length of ICU stay was 12 (IQR 5-22) days; 10 (IQR 4-18) days for women and 13 (IQR 6-24) days for men.

Median follow-up time was 183 (IQR 158-199, range 114-230) days. In total, we observed a crude mortality at 30-days of 23.3%, in women 21.4% and in men 24.0%. Mortality at 90-days was 26.9% for the entire study cohort, 23.4% and 28.2% for women and men respectively. After 90 days until end of follow-up, only 11 deaths occurred. Overall time to death is depicted in figure 1.

In the Cox regression model, male sex, age, cardiac disease, COPD/asthma, diabetes, hypertension, immune deficiency, chronic liver disease. chronic kidney disease, malignancy, SAPS 3 (excluding age and comorbidity components) and admission month were significantly associated with mortality. In the multivariable Cox regression analysis, male sex (HR 1.28, 95% CI 1.06-1.55) remained significantly associated with mortality even after adjustment for the above-mentioned covariates, also including morbid obesity and neuromuscular disease. In addition, age (HR 1.07, 95% CI 1.06-1.08 per year), COPD/asthma (HR 1.46, 95% CI 1.20-1.79), immune deficiency (HR 1.56, 95% CI 1.18-2.07), morbid obesity (HR 1.45, 95% CI 1.05-1.99), malignancy (HR 1.81, 95% CI 1.19 - 2.74), SAPS 3 (HR 1.04, 95% CI 1.03-1.05 per unit increase) and admission month (HR 0.48, 95% CI 0.36-0.63, June vs. March) were also significantly associated with mortality. We could not demonstrate any statistically significant interaction between age and patient sex (figure 2).

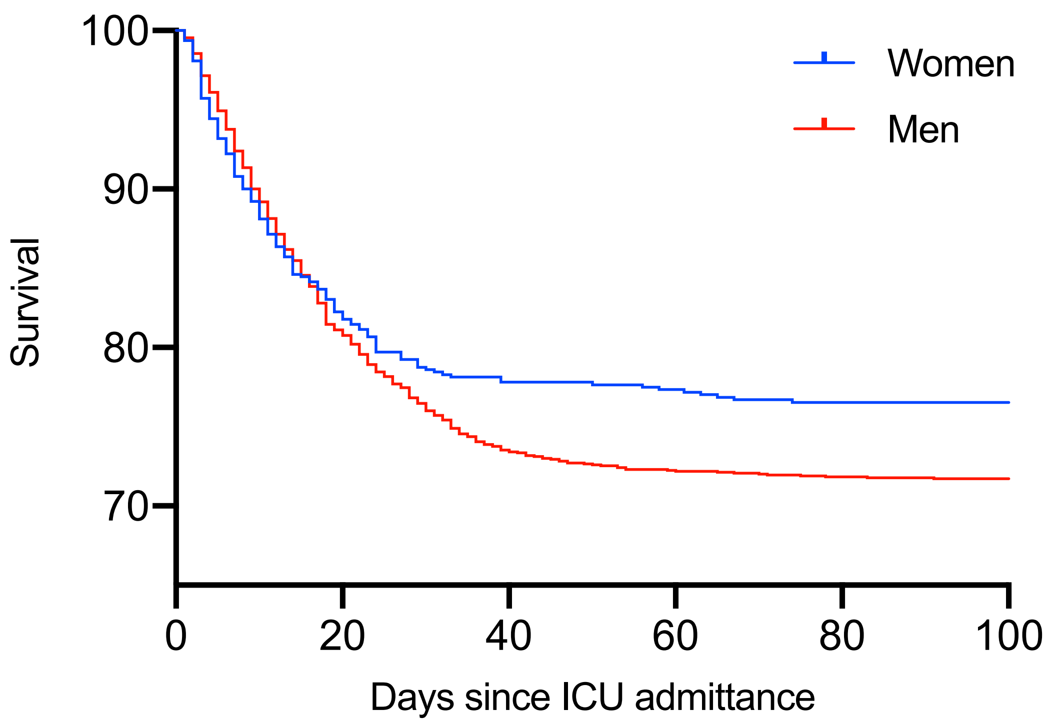

Figure 1. Time to death for men and women admitted to ICU. After 90 days, only 11 more deaths occurred. $p = 0.016$

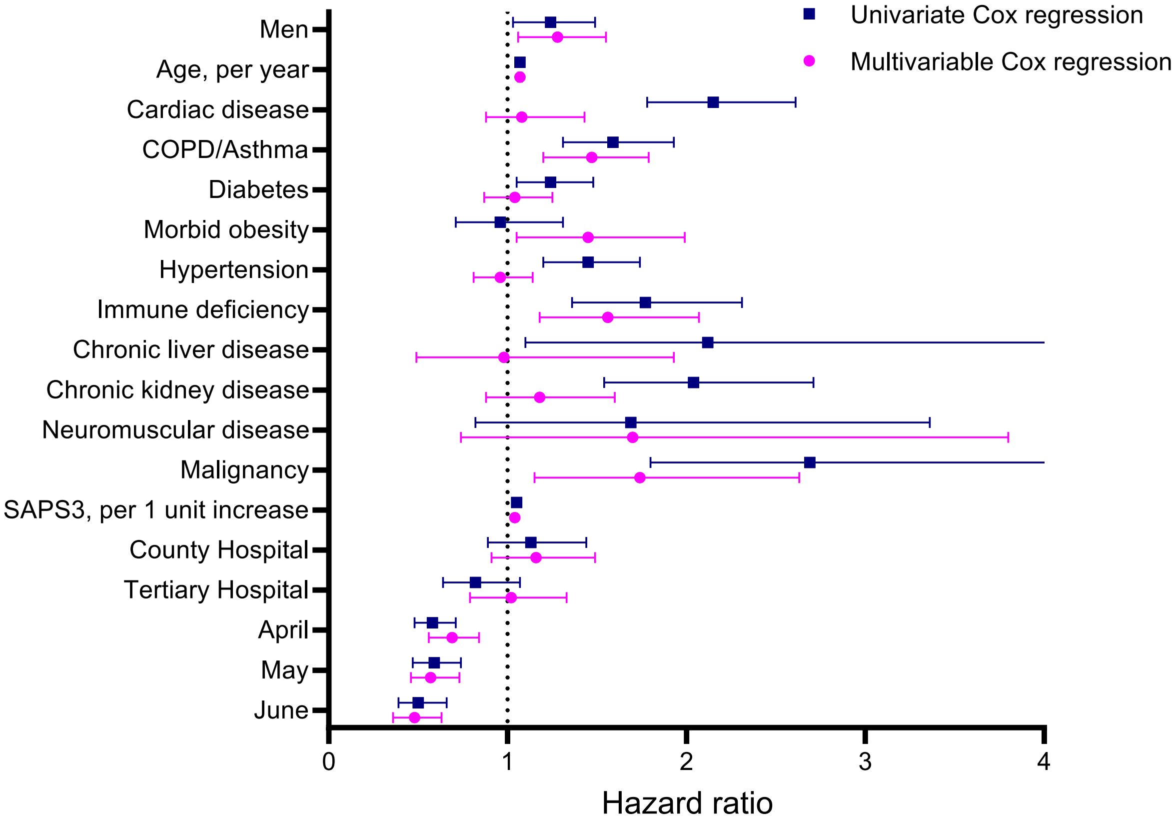

Figure 2. Univariate and multivariable Cox regression exploring 90-day mortality. Local hospital is considered as reference. March is considered as reference month

6 DISCUSSION

6.1 GENERAL DISCUSSION

This thesis is based on one simple question, asked six years ago: “Why are so many ICU patients men?”. At first glance it is easily explained by a few well-known facts; men are more often subject to trauma and trauma patients often end up in the ICU, and men are more prone to develop diseases that require intensive care. This has been previously described in several studies (57–61). However, after removing trauma patients from the equation, there are still more men in the ICU (62,63). And we still did not know if men truly are more prone to develop diseases that require intensive care, or if there is some unknown factor that contributes to the inequity. Hence, the overall aim of this thesis was to investigate why there are more men in the intensive care unit, and if men and women are treated differently whilst in the ICU.

There are more women than men admitted to hospitals in Sweden in general (26), but more men admitted to the ICU (19,23). The first question that needed answering was therefore if the threshold for accessing the ICU differed between men and women, given equal burden of disease. The ideal way of answering this would be to determine the level of illness in all patients in the hospital, and then to investigate which patients were admitted to an ICU. A study of that kind might be possible in the near future, depending on new ways of surveying patients, but at the moment we had to approach it differently. As we did not expect our colleagues to have an explicit bias towards men or women, merely asking our colleagues if they would prefer to admit a man or a woman to ICU would hardly work. On the off chance that physicians do have a patient gender preference, it is not probable that this clouds clinical judgement, given that they are not under severe stress. We had to somehow evoke any potential implicit bias which is more difficult than one might think.

We wanted to investigate if women were less likely to be admitted to ICUs because of implicit bias. Our notion was that if we would randomize responders to one of two identical surveys (where only gender of the patient differed) asking them if they would admit a fictive potential ICU-patient, and also blind them to the true aim of the survey, any difference in admittance rate between the two surveys would be attributable to the only variable that separated them, namely the gender of the patient. This still holds true; if any difference was observed it would likely be caused by gender bias. Hence, the specificity of the test is high. The problem in analyzing the results occurred when it became obvious that there was no difference in admittance between men and women. It is reasonable to assume that the test lacks sensitivity to detect implicit bias. In the most widely used test for implicit bias, the Implicit Association Test (IAT), time is introduced as a variable, with the purpose of removing cognition, making the respondent answer intuitively. This was not a part of our test. Still, there is evidence supporting our approach (64), and the null result is encouraging. We conclude that when exposed to a fictive paper case, Swedish physicians do not exhibit any tendency for gender bias when admitting patients to the ICU. In an effort to sharpen the tool we reconstructed the survey, removing all but one case from study I, keeping only the case that had proved to be the most contentious regarding whether to admit or not. The European Society of Intensive Care Medicine agreed to endorse the study, which they did by assisting in construction of the survey, promoting it and linking to it from their website. Even if we considered results from this survey slightly easier to interpret, we still had reason to believe that we lacked sensitivity and we found no difference in admittance rate between men and women. Furthermore, there was the problem of response rate. In study I, we could approximate response rate by extracting information concerning the number of physicians at each hospital who were likely to be receiving our study. For study II, it was impossible to establish a response rate.

To summarize study I and II, we could not see any difference in ICU-admittance between men and women, but the studies were hampered by lack of sensitivity and high risk of volunteer bias. To our knowledge this has not been studied in this setting previously, but when investigating differences in ICU-admittance between men and women in a trauma cohort it was reported that men were more likely to be admitted to an ICU. The difference was restricted to patients with less severe injury and did not translate to a beneficial effect on mortality. On the contrary, men had a higher risk of mortality overall (65). Similarly, in a large study from Canada, Dodek et al found men to be more likely to be admitted to an ICU even after adjusting for confounders (62).

The next step was to investigate if the discrepancy in ICU population between men and women was caused by differences in ICU length of stay. Could it be that men were given more time in the ICU and that is what caused the discrepancy in ICU population? The principal question that we wanted answered was if given equal disease burden, do men stay longer in the ICU than women? We investigated this by utilizing a data set of approximately 9,000 ICU patients. The challenging part is clearly how to ensure that we compare equally sick patients. For each patient, different severity of illness scores is filled out by the physician. Acute Physiology and Chronic Health Evaluation II (APACHE II) was used by the hospital as severity of illness score until 2010. After 2010 the hospital instead started using Simplified Acute Physiology Score 3 (SAPS 3). These are filled out the day the patient is admitted to the ICU, and its purpose is to predict the mortality risk. Both APACHE II and SAPS 3 have been validated in several different settings (66–68) and proved to have acceptable performance regarding predicting mortality and have showed similar results when compared (69,70). For the purpose of being able to include all patients in the cohort, we decided to treat the estimated mortality risk (EMR) calculated from APACHE II and SAPS 3 as equivalent to each other. But the EMR only gives us a baseline risk, which makes our patients comparable at admission. We also needed some way to compare patients over time, since we are investigating the length of stay. Every day, an additional score is supposed to be filled out by the physician; The Sequential Organ Failure Assessment (SOFA) score. Its purpose is to evaluate the patient's rate of organ failure and its practical use in research to serve as proxy for illness progression. It is frequently used as a mortality prediction model in ICU-patients (71–74). However, filling out SOFA is unfortunately often overlooked, and we had too many missing values for it to be used as intended. Realizing that we were unable to use SOFA was naturally a setback. Luckily, the SOFA score was more frequently filled out on the day of discharge. This gave us the opportunity to use it as a variable (SOFA out). In an effort to minimize the risk of comparing men and women who at baseline were unequally ill, we also used a third scoring system, Charlson Comorbidity Index (CCI). This index is developed for approximating 1-year mortality risk using weighted scores calculated from different comorbidities (75) and has been validated and used in intensive care settings (76–79). With this information we could construct a Fine-Gray competing risk model, treating death in the ICU as a competing risk of being discharged from the ICU using age, sex, EMR, SOFA out and CCI as explanatory variables. We further constructed identical logistic regression models for comparison of 30- and 90-day mortality. From this we learned that men had a slightly lower probability of being discharged, but similar 30- and 90-day mortality. It is not unambiguous how these findings should be interpreted, especially considering that there is no difference in ICU-mortality between men and women. Nevertheless, given that the patient does not die in the ICU, men have a slightly lower probability of discharge from the ICU at any time. The clinical relevance of this is unclear, but results are in concordance with previous research. In a very large study Mahmood et al found a small survival advantage for women <50 years of age, and no difference in mortality between men and women >50 years of age (13). Valentin et al found no difference in mortality following intensive care (15), but disparate results exist (39,42,80,81). These studies are however becoming dated. In a more recent study from Sweden, no difference in mortality was observed (19). We concluded that the main finding of this study was that there were no differences in mortality. This is certainly encouraging. The only remaining question was if there were any differences in the intensity of intensive care offered to men and women.

This led us to our fourth study, where we aimed at investigating differences in the care provided within the ICU. We used the same cohort as in study III, with the exception that readmissions were added. The intensive care items compared are described in methods. For this analysis we decided against using SOFA as an explanatory variable, on the basis of having too much data missing. Interestingly, it appears as if men overall receive more invasive ventilation, vasoactive treatment and renal replacement therapy. In the subgroup analysis we found that men admitted with respiratory diseases received more invasive ventilation, and men admitted with sepsis or after cardiac arrest received more inotropic treatment in the form of levosimendan than women. Similar results have been previously described in multi-center studies from Austria and Canada (14,15). In both studies, women were found to be less likely to receive common intensive care treatments. In contrast to Fowler et al, who found older women to have a slightly increased risk of death in the ICU (14), Valentin et al found no adverse effect on mortality (15).

The outbreak of corona in 2019 causing a pandemic in 2020 and 2021 has resulted in great suffering worldwide. As clinicians working with COVID-19 patients in hastily constructed temporary COVID-19-specific intensive care units, it became clear to us fairly early that a majority of patients were men. Reports from China and Italy confirmed this (82,83), but there was naturally a knowledge gap regarding differences between men and women in long-term mortality, comorbidities and level of care in the ICU. For our final study, we therefore investigated differences in long-term outcomes in women and men following infection with SARS-CoV-2. A majority of patients were men (73.2%) and they had a higher risk of mortality, received more invasive ventilation, renal replacement therapy and were more often placed in prone position. This is somewhat in line with current literature, with several centers reporting more men in their ICUs, and a higher mortality risk for men (83–85). There are to our knowledge no other studies reporting differences in care provided to men and women with COVID-19.

To conclude study III, IV and V it seems as if men need more time and resources in the ICU, but with no positive effect on survival rate. There is a possibility that given equal level of treatment, women would have a survival benefit, assuming that more invasive ventilation, renal replacement therapy and inotropic treatment equals better outcome. *Why* men need more intensive care is however still an enigma. There is by now a fair body of evidence supporting sex-differences in various pathophysiological responses to illness, where men in general seem to develop a more severe response in several different organs (86–91). This is at large explained by differences in sex-hormones (92–95), but this is likely only part of the explanation, as sex-chromosomes, genomic and epigenomic differences also play a part in the regulation of the immune response (96,97). The field is vast and complicated, but there are a few points that require attention:

6.1.1 Respiration and immune response

Men seem to be more at risk for developing severe respiratory symptoms following acute respiratory illness (98,99) and at least there are plausible explanations for differences in development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (99). This is clearly observed in study V and attributed to differences in immune response to viral infection. Both X- and Y-chromosomes have immunoregulatory genes and incomplete inactivation of these genes affect the risk of autoimmune diseases as well as the response to vaccination and virus infection. Sex steroids also have a direct effect on immune cell function, which results in different immune response to disease (100). Similar results have been presented for the development of sepsis, where men had increased level of proinflammatory cytokines and decreased levels of cytokines with anti-inflammatory properties as compared to women (42).

6.1.2 Cardiovascular response

Sex-differences in cardiovascular diseases have been thoroughly investigated (30,101–103), and there is compelling evidence regarding differences in heart failure, that would at least partly explain the differences in use of levosimendan noted in study IV. Men are more prone to develop macrovascular coronary artery disease, commonly leading to heart failure with reduced ejection fraction (HFrEF) while women are more prone to develop endothelial inflammation, leading to microvascular dysfunction, which in turn leads to heart failure with preserved ejection fraction (HFpEF) (104). This will in turn lead to less use of levosimendan in women, since its primary indication is in HFrEF, even if some positive results have been found also in HFpEF (105). Estrogen might play a role as explanatory variable in the pathophysiology of heart failure; treatment with estrogen preserved ejection fraction in rats with heart failure (106) and administration of estradiol post hemorrhagic shock in rats restored their cardiac index to sham levels (107). There also seems to be sex-specific differences in vascular response to illness, as demonstrated by Li et al who found that premenopausal women have a stronger responsiveness in vasoreactivity compared to postmenopausal women and men when investigated in healthy humans. In their rat model, they found that male rats lost more of their vascular reactivity compared to female rats following hemorrhagic shock (108). Infusion of exogen 17-β estradiol increased MAP and animal survival. This may in part justify why women received less vasoactive treatment as compared to men in our study.

6.1.3 Acute kidney injury

Differences in incidence of acute kidney injury (AKI) between men and women have been priorly investigated. Women have been found to be less likely than men to develop AKI (9,109,110) and there is compelling evidence from animal models supporting the role of estrogen to be protective against the development of AKI (111–113). This is in line with our results, where we found that men receive more renal replacement therapy (RRT) then women.

6.2 METHODOLOGICAL CONSIDERATIONS

This thesis is built on epidemiology, where we investigate exposure and outcome in intensive care patients. We aimed at answering questions regarding any sex- and gender differences in intensive care but to be able to interpret the results correctly one must be aware of certain definitions and pitfalls.

6.2.1 Internal validity

Internal validity is defined as to which extent the observed results in a study are accurate, or the result of different types of methodological errors. Within epidemiology, typical systematic errors are bias and confounding. Errors can also be caused by random errors. There are several different types of bias. In this thesis, both different forms of selection bias and information bias are at risk of distorting results. Furthermore, unmeasured confounding can always have a potential influence on results and are by nature difficult to shield from.

6.2.2 Volunteer bias

Volunteer bias is a form of selection bias. It occurs when respondents who volunteer to participate in a study do not represent the target population. A low response rate increases the risk of volunteer bias. As previously mentioned, in study I and II there was a very low response rate. Consequently, the risk of volunteer bias is high in both study I and II.

6.2.3 Measurement error

Measurement error is a form of information bias and occur when we do not measure what we intend to measure. This can be caused be erroneous instruments. In the case of a survey study, it can also occur because of attitudes from the respondent, for example carelessness. There is a risk of measurement error in both study I and II. We think we measure implicit bias, but it is likely that the surveys did not evoke implicit attitudes in the respondents.

6.2.4 Confounding

A confounder is a variable that influences both the independent (X) and dependent (Y) variable, and thereby incorrectly suggests causal effect between X and Y. Known confounders can be predicted and adjusted for with the use of statistical modelling. However, unknown confounders are inherently impossible to correct for and might therefore cause results to be misinterpreted. For studies III-V there is a risk of unknown confounders. Partly because of the complex form of care provided in the ICU; there are a multitude of variables that are unmeasured, which physicians and nurses value when deciding on different ways to treat the patient.

6.2.5 Random error

If an error is not systematic, they are random. They can occur because of mistakes from a respondent or in the collection of data. Since a random error is not repeatable, the impact on results will diminish with a larger sample size. Studies III-V in this thesis were all based on large cohorts, and the risk of random errors is considered to be low.

6.2.6 External validity

The concept of external validity is constituted by the extent to which the results of the study can be generalized beyond the cohort included in the study. External validity is highly dependent on internal validity. If the internal validity is low, external validity will be consequently low. High internal validity however does not guarantee high external validity if, for example, the sample is highly specific and not easily compared to a different cohort. The work that constitutes this thesis is generalizable to populations in countries with similar socio-economic profile and health care systems, i.e., tax-based funded health care. Privately funded health care will introduce other variables that might influence results, for example differences in financial condition and ability to pay between men and women.

7 CONCLUSIONS

This thesis aimed at investigating the entire chain of events surrounding an intensive care episode, from admittance until 90-days post intensive care. Concerning the afferent arm, we did not observe any differences in admittance to the ICU that could be attributable to gender bias. When investigating the efferent arm, we found no differences in mortality. We did however find that men have a lower probability of being discharged from the ICU. Furthermore, we found that men received more intensive care in the form of invasive ventilation, vasoactive treatment and RRT. If admitted with sepsis or post cardiac arrest, men received more inotropic treatment.

In patients admitted with COVID-19, we found that men had a higher long-term mortality, a longer length of stay and received more intensive care resources in the form of invasive ventilation, RRT and being positioned in prone position.

8 POINTS OF PERSPECTIVE

Even if there was an absence of gender bias in this thesis, future research should systematically include sex and gender as variables of investigation. We have historically treated men and women differently within the field of medicine, and even if that might have been medically sound, it is not until now that we have a deeper understanding of the reasons behind differences in treatment. Different people respond differently to disease. Dichotomizing on patient biological sex might be an oversimplification, but it could be an important step when aiming at individualizing treatment.

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