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RESEARCH ARTICLE

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Comorbid burden at ICU admission in COVID-19 compared to sepsis and acute respiratory distress syndrome

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Abstract

Background: Comorbidities are similarly associated with short-term mortality for COVID-19, acute respiratory distress syndrome (ARDS) and sepsis in intensive care unit (ICU) patients, but their adjusted frequencies at admission are unknown. Thus, we aimed to evaluate the adjusted distribution, reported as odds ratios, of known risk factors (i.e., age, sex and comorbidities) for ICU admission between COVID-19, sepsis and ARDS patients in this nationwide registry-based study.

Methods: In this cohort study, we included adult patients admitted to Swedish ICUs with COVID-19 ($n = 7382$) during the pandemic and compared them to patients admitted to ICU with sepsis ($n = 22{,}354$) or ARDS ($n = 2776$) during a pre-COVID-19 period. The main outcomes were the adjusted odds for comorbidities, sex, and age in multivariable logistic regression on diagnostic categories in patients admitted to ICU, COVID-19 or sepsis and COVID-19 or ARDS.

Results: We found that most comorbidities, as well as age, had a stronger association with sepsis admission than COVID-19 admission with the exception of male sex, type 2 diabetes mellitus, and asthma that were more strongly associated with COVID-19 admission, while no difference was seen for chronic renal failure and obesity. For COVID-19 and ARDS admission most risk factors were more strongly associated with ARDS admission except for male sex, type 2 diabetes mellitus, chronic renal failure, and obesity which were more strongly associated with COVID-19 admission, whereas hypertension, chronic obstructive pulmonary disease and asthma were not different.

Conclusions: Patients admitted to ICU with sepsis or ARDS carry a heavier burden of comorbidity and high age than patients admitted with COVID-19. This is likely caused by a combination of: (1) respiratory failure in COVID-19 being less dependent on comorbidities than in other forms of ARDS, and the cause of critical illness in other

infections causing sepsis and (2) COVID-19 patients being deferred admission in situations where patients with the other syndromes were admitted.

KEYWORDS
acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, comorbidity, COVID-19, critical care, diabetes, heart disease, hypertension, sepsis

1 | INTRODUCTION

Corona virus disease 2019 (COVID-19) is in an endemic phase and continues to contribute to intensive care unit (ICU) admissions, long term disabilities and mortality globally.[1] Parallel to COVID-19, non-COVID-19 acute respiratory distress syndrome (ARDS) and non-COVID-19 sepsis affect millions of individuals yearly.[2,3] ARDS is a hypoxic respiratory failure syndrome with multiple causes all affecting the lungs through systemic or pulmonary inflammation.[4] Common causes for ARDS are pneumonia, non-pulmonary sepsis, aspiration pneumonitis and trauma.[2] The sepsis syndrome is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and is a major cause of ICU bed usage.[5] Several risk factors for severe disease and mortality have been proposed in different cohorts regarding COVID-19,[6–9] ARDS[10,11] and sepsis[12,13] including different comorbidities, age and sex. Risk factors for mortality after ICU admission are described to be similar for COVID-19, ARDS and sepsis.[14] Despite this, there is a gap in our understanding of the relative impact of comorbidites, age and sex as risk factors for ICU-admission in COVID-19, ARDS and sepsis. In the present analysis we use the same cohort as in a previous publication in which we analysed mortality after intensive care.[14] Here, we compare the adjusted frequency of risk factors, presented as odds ratios, in ICU admission with COVID-19 compared to non-COVID ARDS, and with COVID-19 compared to sepsis. This additional analysis is important and adds new insight because it explicitly analyses the risk factors of admission and thereby the admission practices, whereas the previous mortality analysis only includes these implicitly while potentially being biased by how far intensive care is continued between patients with different comorbidities. Further, ICU admission affects a much larger proportion of the population and as such is a patient-centred outcome that allows prioritization of preventive measures in wards and analysis of long-term outcomes in survivors.

2 | METHODS

The study was approved by the Regional Ethics Committee of Uppsala (approval no. 2016/421) and the Swedish Ethical Review Authority (approval no. 2020-02144 with revisions). Informed consent was waived by both authorities because of the nature of the study. The research was conducted in accordance with the Declaration of Helsinki with subsequent revisions and its reporting follows the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.[15]

This is a secondary analysis of the cohort used for a retrospectively designed national cohort study with prospective collection of data on the relative importance of risk factors for 60-day mortality in ICU admissions with COVID-19 and ARDS or sepsis.[14] In multivariable logistic regression models adjusting for age sex and comorbidities, we aimed to explore the relative frequency, expressed as odds ratio (OR), of each risk factor for being admitted with COVID-19 compared with ARDS and COVID-19 compared with sepsis.

2.1 | Registries

The Swedish intensive care registry (SIR) is a high-ranking quality registry to which all general ICUs report all ICU admissions.[16,17] We procured data on all ICU admissions during the study periods with a discharge diagnosis compatible with COVID-19, ARDS or sepsis from SIR. The diagnostic coding system International Statistical Classification of Diseases and Related Health Problems—tenth edition (ICD-10) was used by SIR with the code U07.1 for COVID-19. This code indicates a positive polymerase chain reaction to the Severe acute respiratory coronavirus 2. SIR used the American-European consensus conference definitions of ARDS until 2015, from 2016 the Berlin definition was used, ICD-10 code J80.9x. For severe sepsis and septic shock according to the sepsis 2 criteria[18] the ICD-10 code A49.9 was to some extent used in parallel to R65.1 or R57.2 during the study period. The diagnostic coding of COVID-19, ARDS and sepsis is included in the especially important codes of the SIR and there is a specific coding manual included in on-line coding courses available to ICU physicians to this end. The National patient registry (NPR) is managed by the Swedish board of health and welfare and, according to Swedish law, all inpatient and all outpatient visits in specialized care are reported to the NPR. The NPR provided data on previous health care encounters with dates, diagnoses and basic demographics. The validity of the coding is deemed to be high,[19] however primary care is not included.

2.2 | Participants

We included adult ICU patients with a COVID-19 discharge diagnosis, an ARDS discharge diagnosis, or a severe sepsis or septic shock discharge diagnosis. Patients were included on their first eligible ICU

admission, and admissions separated by <24 h were merged. In order to separate the COVID-19 group from the ARDS and sepsis groups we included COVID-19 patients from 6 February 2020 to 16 June 2021 and compared them to a convenient sample of historical ARDS and sepsis patients admitted to ICU from 2011 to 2016. This meant that we allowed ARDS patients to be included in the sepsis group and vice versa. As the COVID-19 patients, and the ARDS and sepsis patients stem from different cohorts the COVID-19 patients may have been previously included in the ARDS and/or sepsis cohorts as well. Inclusion criteria were discharge (alive or dead) from a Swedish ICU with the aforementioned diagnoses and ICU admission in the previously mentioned time spans. Exclusion criteria were lack of a valid personal identification number (PIN) or age <18 years.

2.3 | Statistics

The primary outcome was the relative importance, OR, of age, sex, and specified comorbidities (Table S1, Supplemental digital content, online) for ICU admission with COVID-19 or ARDS and COVID-19 or sepsis. The present analysis assumes that the population at risk is a large part of the population that were exposed to the pathogens under study at random. Thus the denominators for all of the cohorts are the same and a separate control group is not needed for the direct comparison of the groups using multivariable binary logistic regression. We calculated separate models for OR of being a COVID-19 versus an ARDS patient, and a COVID-19 versus a sepsis patient, and thereby estimate the relative importance of comorbidities, sex and age for developing critical illness in patients exposed to the causative pathogens. We used restricted cubic splines for age as we could not rule out a non-linear relationship with the logit of the outcome. The OR of age is thus calculated between the 1st and 3rd quartile. There were indications of multicollinearity between two of the age splines in both models. Due to an imbalance between groups with regard to hospital type, we added this to the models. There were no missing data.

2.4 | Sensitivity analyses

We performed a sensitivity analysis without the hospital type variable in the models as this was added post hoc. Furthermore, the large overlap between the sepsis and ARDS groups was addressed by excluding overlapping patients in a second set of sensitivity analyses.

Data are reported as numbers with (percent) or medians with interquartile range (IQR) expressed as (25th to 75th percentile), as appropriate. A two-sided *P*-value <0.05 was considered statistically significant. When comparing crude differences, the Mann–Whitney *U* test or the Chi2-test was used as appropriate and, Bonferroni adjustment was performed to address multiple comparisons. We performed data management and descriptive statistics with SPSS for Windows version 27 (Microsoft Corp., IL). Binary logistic models and graphics were performed in the R Software version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) with the rms, Hmisc, and forest plot packages.

3 | RESULTS

From SIR we enrolled 7382 consecutive adult ICU patients with a COVID-19 diagnosis. Of these, 19% were also coded with sepsis and 74% with ARDS at discharge from the ICU, however these patients were not included in the ARDS or sepsis groups. We included 2776 patients in the ARDS group and 22,354 patients in the sepsis group. Of these, 1100 patients were included in both the ARDS and the sepsis groups (Figure 1).[14] The ARDS and sepsis patients were numerically older, had a higher updated Charlson Comorbidity Index,[20] and a higher proportion of female sex (Table 1) than the COVID-19 patients.[20,21] Moreover, the ARDS and sepsis patients had substantially higher SAPS3 and SAPS3 box III scores than the COVID-19 patients (*p* values <0.001).

The crude proportion of all studied comorbidities was higher in the ARDS patients than in the COVID-19 patients except for type 2 diabetes mellitus (T2DM), chronic renal failure, asthma, and obesity. In sepsis patients, all studied comorbidities were more common than in the COVID-19 patients (Table 2).

3.1 | Odds for ICU admission

Multivariable binary logistic regression on ICU-admission with COVID-19, ARDS, or sepsis indicated that higher age was more strongly associated with ARDS and sepsis than COVID-19. Male sex showed a stronger association with COVID-19 than ARDS or sepsis. Regarding comorbidities, ischemic heart disease (IHD), non-IHD, type 1 diabetes mellitus (T1DM), stroke, immunosuppression, cancer, haematological malignancy, systemic inflammatory disease, and solid organ transplant had a stronger association with ARDS and sepsis than COVID-19. Hypertension and chronic obstructive pulmonary disease (COPD) showed a stronger association with sepsis than with COVID-19. Chronic renal failure, T2DM and obesity showed a stronger association with COVID-19 than ARDS, while T2DM and asthma were associated with admission for COVID-19 rather than sepsis (Figures 2 and 3).

3.2 | Sensitivity analyses

We performed two sets of sensitivity analyses. First, we excluded the sepsis patients with an additional ARDS diagnosis and vice versa. In the model on COVID-19 and sepsis there were no differences between the main and the sensitivity analysis (Table S2), but in the model on COVID-19 and ARDS, COPD changed to being differential between groups (Table S3). Second, the models were also performed without the variable denoting hospital type. In the model on ICU admission with COVID-19 or sepsis, solid organ transplant recipients

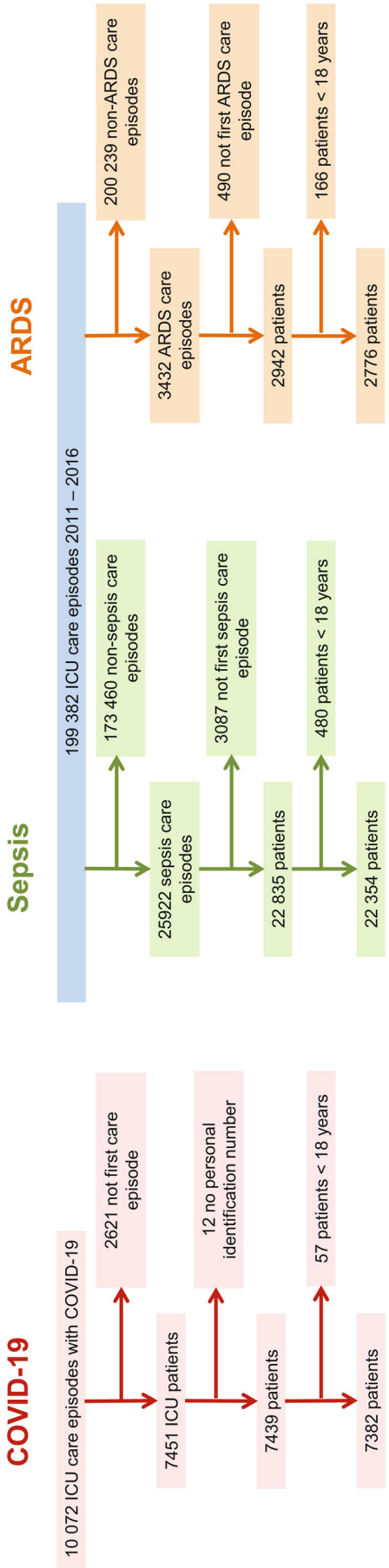

FIGURE 1 Patient selection flowchart. Patients 18 years or older that were admitted to Swedish ICUs were selected for this study from the Swedish Intensive Care Registry. COVID-19 patients admitted between 6 March and 16 June 2021 were included. Patients with non-COVID-19 sepsis or non-COVID-19 ARDS from 2011 to 2016 were included as controls. ARDS, acute respiratory distress syndrome; COVID-19, corona virus disease 2019; ICU, intensive care unit. We used the same cohort for a previous study and the figure is adapted and reprinted under a Creative Commons Attribution 4.0 International License.[14]

ceased to be differential between groups (Table S4). For the model on ICU admission with COVID-19 and ARDS, COPD became differential between groups (Table S5).

4 | DISCUSSION

In this nationwide cohort study on the adjusted relative frequency, expressed as OR, of risk factors for ICU admission in COVID-19, ARDS, and sepsis the key finding is that patients admitted to ICU with COVID-19 are less burdened with comorbidity and age. This can be interpreted as that healthier and less aged patients are selected to receive care in the ICU in COVID-19 than in ARDS or sepsis. As we have previously shown that the association of burden of comorbidity with 60-day mortality is almost equal between COVID-19 and ARDS as well as sepsis,[14] the present findings might indicate that it would be prudent to consider less healthy patients with COVID-19 for admission to ICU than what was practiced in Sweden during the first 1.5 years of the pandemic. Alternatively, the findings might indicate that the severity of COVID-19 does not depend as heavily on comorbidities to cause critical illness, whereas patients with a lower burden of comorbidities are almost never treated in the ICU with sepsis or ARDS. This way of arguing can also be used for sex, which we know is not a cause for the selection of ICU patients in Sweden. A third explanation for our finding may be a differential selection of patients for intensive care, where patients with more comorbidities were excluded from intensive care during the COVID-19 pandemic. However, this would not be explained by a higher acute disease severity as the SAPS3 variables were substantially lower in the COVID-19 patients than in the ARDS and sepsis patients. As a fourth explanation, some hospitals may have used the ICU as a means for infection control through cohort care, that is, using ICU beds for non-critically sick patients. However, this seems unlikely given the resource-intensive nature of ICU care.

To our knowledge, the relative importance of risk factors has not been compared in this setting; however, the explored comorbidities, sex and age have previously been studied in COVID-19, sepsis and ARDS, separately. T2DM was more strongly associated with COVID-19 ICU admission than sepsis or ARDS ICU admission. Accordingly, T2DM has been linked to critical COVID-19,[8,22,23] and to sepsis,[24] but has previously been associated with a lower risk of ARDS,[25] which may explain the greater odds for admission with COVID-19 than ARDS. Further, asthma showed a stronger association with COVID-19 than sepsis, which is consistent with previous findings in COVID-19[8,26,27] combined with a protective effect in sepsis.[28] However, we found no difference in the strength of association for asthma with ICU-admission between COVID-19 and ARDS patients, possibly related to the joint pathophysiology in COVID-19 and ARDS of other aetiologies.[29] Chronic renal failure showed a stronger association with COVID-19 than ARDS in ICU-admission although previous reports show conflicting evidence regarding the impact of chronic renal failure on COVID-19 disease severity.[30] We find no previously published data on chronic renal failure as a risk factor of ARDS development,

TABLE 1 Baseline characteristics of patients included in the COVID-19, sepsis and ARDS groups.

	COVID-19 patients admitted to ICU	ARDS patients admitted to ICU	Sepsis patients admitted to ICU
Number of patients	7382	2776	22,354
With COVID-19	7382 (100)	0 (0)	0 (0)
With sepsis	1389 (18.8)	1100 (39.6)	–
With ARDS	5491 (74.0)	–	1100 (4.9)
Female sex	2191 (29.7)	1033 (37.2)	9500 (42.5)
Age at ICU-admission (years)	63 [53 to 72]	65 [53 to 74]	70 [60 to 78]
Hospital type			
University	2566 (34.8)	1167 (42.0)	5676 (25.4)
County	3749 (50.8)	1211 (43.6)	11,080 (49.6)
District	1067 (14.5)	398 (14.3)	5598 (25.0)
SAPS3	54 [48 to 61]	66 [57 to 76]	66 [57 to 76]
SAPS3 box III	9 [0 to 14]	15 [10 to 21]	16 [10 to 22]
CCI	0 [0 to 1]	1 [0 to 2]	1 [0 to 3]
Surgical admission	130 (1.8)	176 (6.3)	2468 (11.3)

Note: Baseline characteristics of patients ≥18 years old admitted to Swedish ICUs, with COVID-19, between 6th of March and 16th of June 2021 or admitted to Swedish ICUs with non-COVID-19 Sepsis or non-COVID-19 ARDS between the years 2011 and 2016. Data are presented as numbers with (percentages) or medians with [interquartile ranges] as appropriate. ICU, intensive care unit; COVID-19, Coronavirus disease 2019; SAPS3, Simplified Acute Physiology Score 3[21]; CCI, updated Charlson Comorbidity Index[20]; We used the same cohort for a previous study and the table is reprinted under a Creative Commons Attribution 4.0 International License.[14]

TABLE 2 Characteristics of ICU stay and comorbidities of included patients.

	COVID-19 admitted to ICU	*p*	ARDS admitted to ICU	*p*	Sepsis admitted to ICU
Number of patients	7382		2776		22,354
ICU length of stay	7.71 [3.2 to 17.6]	0.22	8.9 [4.0 to 17.7]	<0.001	2.63 [1.1 to 6.7]
Invasive mechanical ventilation	1074 (60.7)	<0.001	2160 (77.8)	<0.001	8494 (38.4)
Ischemic heart disease	518 (7.0)	<0.001	383 (13.8)	<0.001	4352 (19.5)
Non-ischemic heart disease	812 (11.0)	<0.001	602 (21.7)	<0.001	7025 (31.4)
Hypertension	1739 (23.6)	<0.001	913 (32.9)	<0.001	9504 (42.5)
Diabetes mellitus type 1	74 (1.0)	<0.001	140 (5.0)	<0.001	1398 (6.3)
Diabetes mellitus type 2	944 (12.8)	0.81	397 (14.3)	<0.001	4408 (19.7)
Stroke	211 (2.9)	<0.001	260 (9.4)	<0.001	2845 (12.7)
Chronic renal failure	282 (3.8)	>0.99	124 (4.5)	<0.001	1664 (7.5)
COPD	279 (3.8)	<0.001	171 (6.2)	<0.001	2344 (10.5)
Asthma	306 (4.1)	>0.99	125 (4.5)	<0.001	1266 (5.7)
Obesity	333 (4.5)	>0.99	106 (3.8)	0.009	1243 (5.6)
Immunosuppressed	38 (0.5)	<0.001	131 (4.7)	<0.001	661 (3.0)
Cancer	122 (1.7)	<0.001	242 (8.7)	<0.001	2257 (10.1)
Haematological malignancy	78 (1.1)	<0.001	192 (6.9)	<0.001	986 (4.4)
Inflammatory disease	283 (3.8)	<0.001	246 (8.9)	<0.001	2412 (10.8)
Solid organ transplant recipient	88 (1.2)	0.036	56 (2.0)	0.015	395 (1.8)

Note: Outcome and comorbidities of patients ≥18 years old admitted to Swedish ICUs, with COVID-19, between 6th of March and 16th of June 2021 or admitted to Swedish ICUs with non-COVID-19 Sepsis or non-COVID-19 ARDS between the years 2011 and 2016. Data are presented as numbers with (percentages) or medians with [interquartile range]. *p* is *p* value, after Bonferroni adjustment, for difference between COVID-19 and the column to the right of the *p* value. We used the same cohort for a previous study and the table is reprinted under a Creative Commons Attribution 4.0 International License.[14]

Abbreviations: ARD, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, Corona virus disease 2019; ICU, intensive care unit.

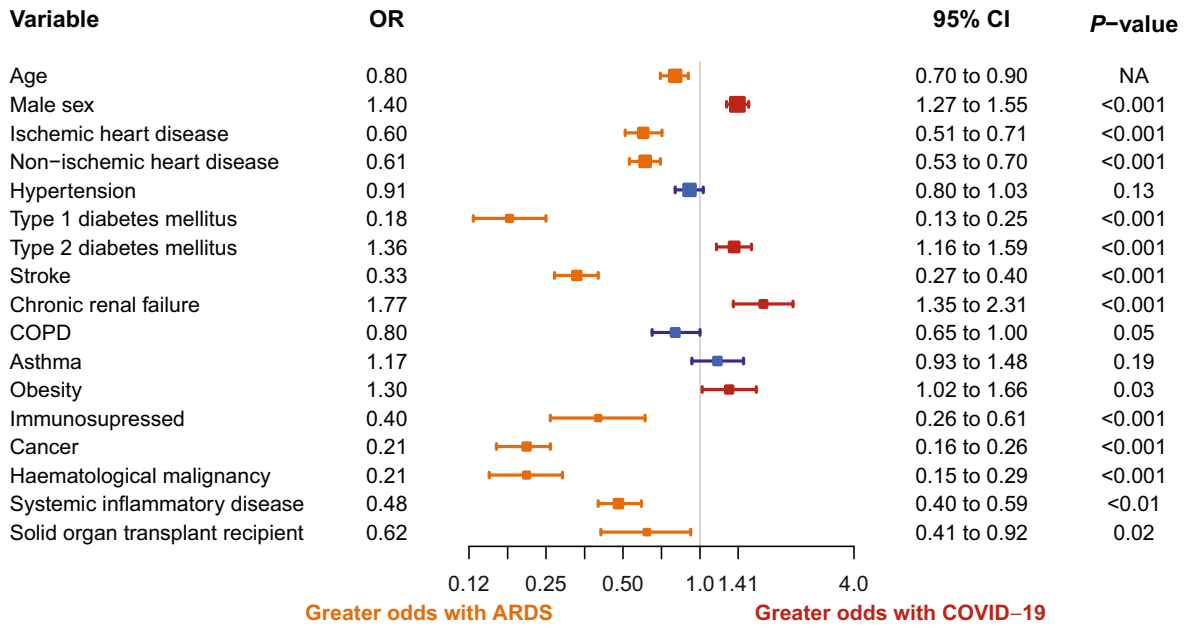

FIGURE 2 Risk factors for ICU admission with ARDS compared to COVID-19. Increasing OR indicates an increasing probability to be admitted with COVID-19 contra ARDS in a logistic regression model. ARDS is ARDS without COVID-19. A *p* value <0.05 indicates a differential effect of a risk factor between ARDS and COVID-19. ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, corona virus disease 2019; ICU, intensive care unit. Also in model: Hospital type District—County: OR 0.89 (95% CI 0.77 to 1.02), and University—County: OR 0.74 (95% CI 0.67 to 0.82).

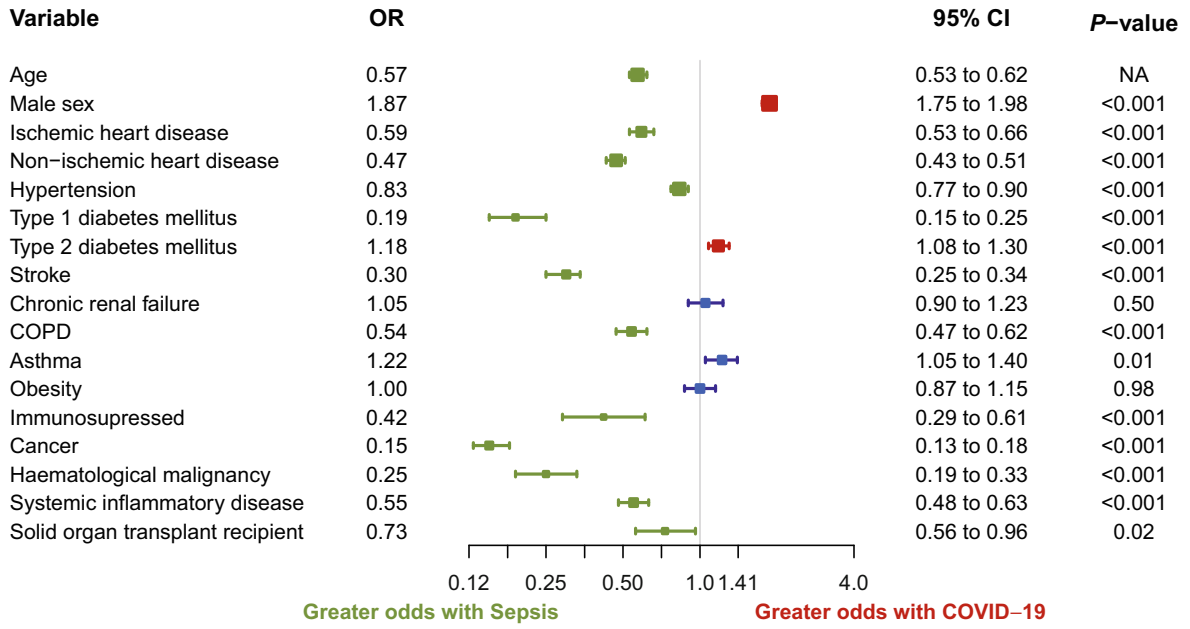

FIGURE 3 Risk factors for ICU admission with Sepsis compared to COVID-19. Increasing OR indicates an increasing probability to be admitted with COVID-19 contra sepsis in a logistic regression model. Sepsis is severe sepsis or septic shock without COVID-19. A *p* value <0.05 indicates a differential effect of a risk factor between sepsis and COVID-19. COPD, Chronic obstructive pulmonary disease; COVID-19, Corona virus disease 2019; ICU, Intensive care unit. Also in model: Hospital type District—County: OR 0.60 (95% CI 0.55 to 0.65) and University—County: OR 1.31 (95% CI 1.23 to 1.40).

however, the Lung Safe study reported a chronic renal failure prevalence of 10% in ARDS patients which is similar to our crude findings. Obesity was associated with COVID-19 admission rather than ARDS, which is expected given the strong association between body mass index and disease severity in COVID-19.[31] The vast majority of the other comorbidities showed a stronger association with ICU

admission with ARDS and sepsis than COVID-19. For example, heart disease, both ischemic and non-ischemic, was more strongly associated with ARDS and sepsis than COVID-19. This finding agrees with previous findings on heart disease as a risk factor for sepsis.[32] In addition, in a previous study on a similar COVID-19 cohort which was compared to population controls, we found no association to heart disease.[8]

We report a weaker association between age and ICU-admission in COVID-19 than in ARDS and sepsis. One possible interpretation is that advanced age is not a particularly strong predictor for severe disease in COVID-19. However, the stronger association between age and ICU-admission in both sepsis and ARDS compared with COVID-19 may also partially be explained by a large variability of admission policies during the surges of COVID-19 likely not present during the period from which the sepsis and ARDS patients were included.[33] Restrictive admission policies for the elderly might be driven by the considerably longer ICU stay in COVID-19 patients than in sepsis and ARDS patients. Such restrictions may have also led to a biased selection of older patients with COVID-19 compared with older patients with sepsis and ARDS, which may, in turn, affect our statistical models despite efforts to control for comorbidities. In our data, male sex has a stronger association with COVID-19 ICU admission than sepsis and ARDS ICU admission. This association is driven by 79% of the COVID-19 ICU admissions in Sweden being men, indicating that they have a much higher risk of severe disease than women. However, the association is damped by a greater proportion of men in ICU admission for any cause including sepsis and ARDS.[13,34] Moreover, male sex is an established risk factor for severe COVID-19 disease[35,36] and the underlying biological processes are under investigation.[37]

The major *strength of this study is the nationwide setting facilitated by the Swedish PIN system and the high-quality* registries that provided the data on this large cohort. Moreover, the outcome measure, that is, ICU admission combined with discharge diagnoses which are logged for all general ICUs in Sweden leaves little room for outcome misclassification.[38] Furthermore, we were able to validate the COVID-19 diagnosis between two sub-registries of the SIR. Finally, the comorbidities under study are captured by a governmental registry to which reporting is mandatory, thus minimizing the risk of exposure misclassification.

There are some inherent limitations to observational studies that may have been aggravated during the COVID-19 group at the height of the pandemic. Despite the continuous monitoring of the registries, data for the COVID-19 group was reported to us before full quality checks and may thus include more errors than the historical controls. Even so, the comorbidities were mainly recorded in the pre-pandemic era. In addition, patients may have had specific comorbidities that were not coded into the registries, either because they were only coded in primary care or because they were not coded at all. In the present setting, the sepsis definitions have changed somewhat from the Sepsis 2 to Sepsis 3 framework. However, the differences between the former severe sepsis and the present sepsis are small.[5] Furthermore, the differences in the distribution of risk factors might partially be attributed to virus epidemiology. Large numbers of middle-aged individuals with limited comorbidity were exposed to, and infected by, the Severe Acute Respiratory Syndrome-corona virus-2, and a minority also developed a critical illness. Many older individuals with more marked comorbidity have practiced self-isolation and thus may have avoided infection, and the most frail, in need of extensive help with activities of daily living, are usually withheld admission to intensive care. However, we mean that the exposure to bacteria, viruses and trauma is similar enough between individuals to allow for meaningful comparisons between admission groups, a reasoning successfully exploited in genetic and proteomic studies.[39,40] In addition, despite indications of multicollinearity in association to age the variable was kept in the models as it would be futile to model without it. Age is a very important confounder with extensive effects on both comorbidities and organ dysfunction.[41,42]

4.1 | Conclusions

In conclusion, we find that the burden of age and comorbidity is more prominent in ICU-admission for sepsis and ARDS than for COVID-19. This is likely to be caused by a combination of COVID-19 affecting the relatively healthy more severely, that is, the cause of respiratory failure is not as strongly dependent on comorbidities as in other forms of ARDS, and the use of restrictive admission policies during the early part of the pandemic in severely affected areas.

AUTHOR CONTRIBUTIONS

BA, RF, IML, GS, ML, and MH conceived and designed the study; BA and ML acquired the data. BA and MH analyzed the data; BA and MH drafted the manuscript; and BA, RF, IML, GS, ML, and MH finalized the manuscript. All authors approved the final manuscript as submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the respective national registries with restrictions as defined by the General Data Protection Regulation (GDPR), the Swedish Personal Data Act (1998:204), and the licenses with the respective national

registries, and so are not publicly available. Data are however available from the authors upon reasonable request after adequate permissions from the Swedish ethical review authority and under the restrictions outlined above.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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