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Interhospital transports and mortality in patients with critical COVID-19: a single-centre cohort study

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ABSTRACT

Objectives

This study aimed to compare mortality rates and length of hospital stay between patients with critical COVID-19 who were transferred to another hospital due to capacity constraints and those who remained at their initial admission hospital.

Design

Single-centre cohort study

Setting and participants

Six hundred and sixty-five patients treated for SARS-CoV-2 at two intensive care units (ICU) in X from 1 March 2020 to 30 June 2021. Data on interhospital transfers were retrieved from medical records and patient data management systems according to pre-defined protocols.

Main outcome measures

The outcomes were 30- and 90-day mortality, days alive and out of ICU. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazard models with adjustments for age, sex, body mass index, severity of illness, comorbidity, invasive ventilation, treatment limitations and pandemic waves.

Results

Of 665 patients, 133 (20%) were transferred to another hospital. The mortality rate for transferred patients compared to non-transferred patients at 30 days was 19% versus 26% (p=0.13), and at 90 days 26% versus 30% (p = 0.43). In the adjusted Cox regression analysis,

interhospital transfer was associated with a lower mortality risk at 30 days (HR 0.47, 95% CI: 0.30–0.76) and 90 days (HR 0.52, 95% CI: 0.34–0.79). However, the number of days alive and out of ICU was significantly lower for the IHT group at 30 and 90 days.

Conclusion

This study indicates that interhospital transfer due to capacity constraints among patients with critical COVID-19 was associated with lower mortality but an extended length of ICU stay. The latter was probably due to the need for invasive ventilation among transferred patients, not the transfer per se. Suitability for transfer may be associated with lower mortality, but residual confounding cannot be excluded.

Strengths and limitations of this study

- The strengths are the comprehensive data collection conducted by dedicated researchers during the three pandemic waves and validated by independent researchers.
- The low proportion of missing data, and the adjustment for known confounders in the analyses.
- The main weaknesses are the single-centre non-randomised design.
- There may be a risk of selection bias in the study since it is likely that stable patients with recovery potential were selected for transport.
- Information about the severity of illness immediately before transport was not readily available in our cohort.

BACKGROUND

Transports of critically ill patients between intensive care units (ICUs) across hospitals are relatively common. The primary reasons include the need to transfer to a hospital with specialised competence, as well as capacity constraints at the transferring hospital (1-3). Regardless of the reason for the transport, studies have shown that patient transfers entail direct risks related to the transport itself and can be linked to delayed diagnostics or treatments (1, 4-8). In X, where the ICU beds per capita are among the lowest in Europe (9), approximately 600 ICU patients are transported between hospitals each year due to a lack of resources at the sending ICU (10). During the COVID-19 pandemic, the influx of patients requiring ICU treatment significantly increased interhospital transfers (IHTs) (10). Studies investigating the risk of IHT during the COVID-19 pandemic have shown conflicting results. Some studies indicate that IHT is not associated with an increased mortality risk (2, 11-14) or may even be associated with a lower risk of death (15), whereas others have shown that IHT is associated with a longer duration of mechanical ventilation (11-13), ICU stay (12) and length of hospital stay (2, 12, 13). None of these studies were randomised controlled trials, and many were limited by a small sample size (2, 11, 14). Despite the large increase in ICU beds in Sweden during the pandemic, a substantial proportion of critically ill patients were transferred between hospitals. To the best of our knowledge, no study has so far studied the influence of IHTs on patient outcomes during the COVID-19 pandemic in X. Therefore, we aimed to compare mortality rates and length of hospital stay between patients who were transferred to another hospital due to capacity constraints and those who remained at their initial admission hospital.

METHODS

Study design

This study included all adult patients (age ≥18 years) with confirmed SARS-CoV-2, as verified by polymerase chain reaction test, requiring intensive care at X Hospital (X) in X, X, between 1 March 2020 and 30 June 2021. The hospital is a secondary referral centre with a large emergency department and a total capacity of 600 beds. Normally, there are 18 beds dedicated to intensive care. However, during the COVID-19 pandemic, the ICUs expanded to accommodate a total of 60 ICU beds. The study was approved by the Regional Ethical Review Board X, X (Dnr: 2023-01778-01-380347, amendment 2023-01778-01), and the requirement for written informed consent from patients was waived. The reporting of the study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (16).

Cohort

Adult patients admitted to the ICU due to SARS-CoV-2 as the primary diagnosis (ICD codes JA36 and U07.1) were eligible for the study. Patients who were transported for reasons other than capacity constraints (e.g. repatriation or clinical transfers) were excluded from the study. Patients were identified using the patient data management system. Clinical data were automatically and manually extracted from medical records and the patient data management system using a pre-defined data collection protocol to ensure consistency and uniformity of the data collection. Cross-validation of data from randomly selected patients was performed separately by two independent researchers.

Exposure

The exposure was IHT, defined as unit-to-unit capacity transfer, with the patient discharged from the ICU at X Hospital and admitted to an ICU at another hospital. The IHTs adhered to the transport recommendations issued by the X Society for Anaesthesia and Intensive Care (17). The selection of patients for transfer due to capacity constraints was commonly done in dialogue with the admitting ICU. The decision was based on whether the patient's physiological status allowed for safe transport, and on the admitting hospital's ability to provide the required care. The actual transport was prepared according to local routines for transports, and handover was reported by telephone. ICU patients in X are commonly transported between hospitals using a mobile intensive care unit (MICU). A MICU is staffed with one ambulance nurse, one paramedic and one physician from the departing intensive care unit. The MICU transporter is more spacious than a standard ambulance, and is equipped with continuous electrocardiography monitoring, invasive hemodynamic monitoring and advanced ventilatory support. Information about the date, time and reasons for transfer was obtained from the patients' medical records and the patient data management system.

Outcomes

The outcomes were mortality at days 30 and 90 from ICU admission and days alive and out of ICU. Length of ICU stay was measured from the date of ICU admission to the date of discharge from ICU at X Hospital or the admitting hospital.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables are expressed as numbers and proportions (percentages). The distribution of continuous variables was tested with the Shapiro-Wilk test. Differences between groups were analysed using the Mann-Whitney U test and the Chi^2 test for continuous and categorical variables, respectively.

In the survival analyses, patients were followed up from the date of ICU admission until the date of death or until 30 and 90 days had passed since admission. Kaplan–Meier curves were used to estimate the cumulative risk of death, and the log-rank test was employed to compare patients with exposure to IHT versus those without IHT. Cox proportional hazards regression was used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) for death within 30 and 90 days from ICU admission. Multivariate models were adjusted for age (continuous), sex (male/female), body mass index (<30/≥30 kg/m^2), Simplified Acute Physiology Score III (SAPS III) (>50/50–59/≥60), Charlson Comorbidity Index (categorised as 0/1/2) (18), invasive mechanical ventilation (yes/no), treatment limitations (yes/no), COVID waves (first wave, March to September 2020 versus second and third waves, October 2020 to January 2021 and February to June 2021 (19)) and IHT (yes/no). Both crude and multivariable models were investigated with no IHT as the reference group. Scaled Schoenfeld residuals were regressed against survival time to assess the proportional hazard assumptions, and Martingale residual plots, together with the Grambsch-Therneau test, were used to assess evidence of non-linearity. Variance inflation factors were used when investigating multicollinearity. All variables were complete except for SAPS and BMI

which were missing for 105 and 6 patients, respectively. This was handled by a separate category for patients with missing values.

To assess the robustness of the findings and potential variations in the data, we performed sensitivity analyses on subgroups of patients based on length of ICU stay (more than 6, 8, 10 and 12 days), mechanical ventilation and COVID waves. Comparisons of days alive free from ICU were conducted using the Mann-Whitney U test and presented as medians with interquartile ranges (IQRs).

A two-sided p-value less than 0.05 was considered statistically significant. The analysis followed a predefined protocol and was conducted using the IBM SPSS Statistics version 29 statistical software and R version 4.3.3 (R Core, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). All analyses were discussed and confirmed with an experienced biostatistician.

RESULTS

Patient cohort

Of 2622 critically ill patients admitted to the two ICUs during the study period, 679 had a confirmed SARS-CoV-2 diagnosis. Nine patients were transported to other hospitals for tertiary care (e.g. ECMO) and five were repatriated to their home region. In total, 665 SARS-CoV-2 patients were included in the study, of which 133 (20%) underwent interhospital transports due to capacity constraints (Figure 1). All patients (n=133) were transported to a hospital within a 30-kilometer radius or maximum of 30 minutes.

The median age of included patients was 64 years, and most were men (72%). Patients who were transferred were more often on mechanical ventilation (98%) compared with the non-transferred patients (40%), and fewer had limitations in terms of life-sustaining treatment (4% versus 15%). Otherwise, the groups were balanced regarding patient and clinical characteristics (Table 1). The median day of IHT from admission was 6 (IQR: 3–11).

Interhospital capacity transfer and mortality

Analyses of IHT and mortality in patients with critical COVID-19 are shown in Table 2. Mortality rates did not differ between groups at either 30 days (19% vs. 26%, p = 0.13) or 90 days (26% vs. 30%, p = 0.43). This was consistent across the log-rank test for survival for 30 days (Supplementary figure 1, p = 0.06) and 90 days (Supplementary figure 2, p = 0.2), as well as the HR of the univariate Cox regression of 0.66 (95% CI: 0.43–1.02) for 30-day mortality and 0.79 (95% CI: 0.54–1.14) for 90-day mortality. When the exposure of IHT was

analysed in the multivariate model, it was associated with a lower risk of mortality for both 30 days (HR 0.47, 95% CI: 0.30–0.76) and 90 days (HR 0.52, 95% CI: 0.34–0.79) (Table 2).

As the assumptions of proportional hazards were violated when scaled Schoenfeld residuals were regressed against survival time ($p < 0.001$ for the multivariate model for 30- and 90-day mortality), sensitivity analyses were performed. When splitting the time and analysing by different lengths of stay (LOS) at the ICU, the assumptions were fulfilled for patients with a LOS of eight days and above ($p = 0.14$ for 30-day mortality and $p = 0.09$ for 90-day mortality). The results did not differ from the original models except for IHT being associated with lower 30-day mortality, including in the univariate analyses for patients with an ICU LOS of more than six and eight days (Table 3). Schoenfeld residuals indicated violations of proportional hazard assumptions, including for the covariates of mechanical ventilation, treatment limitations and COVID-19 wave in the multivariate models for 30 and 90 days. This issue was addressed by examining the various categories within these variables as subgroups. The reason for the violation of the variables of mechanical ventilation and treatment limitations was a small number of patients/events in the groups of patients without mechanical ventilation exposed to IHT and the group with treatment limitations exposed to IHT. When analysing the subgroup of only mechanically ventilated patients, the results changed in the univariate models, showing a lower risk of mortality for 30 days (19.3% versus 32.9%, p=0.008) and 90 days (26.0% versus 38.0%, p=0.029) in the IHT group compared to the non-IHT group. In the multivariate models, the decrease in mortality for the IHT group at 30 and 90 days remained unchanged. Excluding patients with treatment limitations did not change the results.

The results differed between patients treated in the first COVID-19 wave and those treated in the second or third waves. For patients in the first wave, all models – both univariate and multivariate – showed that IHT was associated with lower HR of mortality at 30 and 90 days. By contrast, no significant differences in mortality were observed between the IHT exposure groups in the second and third COVID-19 waves for any of the models. More details regarding the subgroup analyses can be found in Supplementary Files 4-6.

Interhospital transfer and days alive free of ICU

Compared with non-IHT patients, IHT patients had in median fewer days alive and free from the ICU at 30 days (5, IQR: 0–18 versus 22, IQR: 0–27, p<0.001) and 90 days (64, IQR: 27–78 versus 81, IQR: 6–87, p=0.86) respectively (Supplementary figure 3). However, for mechanically ventilated patients, there were no statistically significant median differences between the groups at 30 days (5, IQR: 0–18 versus 2, IQR: 0–16, p=0.31) or 90 days (63, IQR: 24–78 versus 60, IQR: 0–75, p=0.14).

DISCUSSION

In this study, transfers solely due to capacity constraints during the COVID-19 pandemic were not associated with a higher risk of 30- and 90-day mortality among patients with critical COVID-19. Our results indicated that such transfers may even be associated with a reduced mortality risk, especially for mechanically ventilated patients. Interhospital transfer was associated with a longer ICU LOS compared with patients who remained in the admitting ICU. This was probably explained by the higher prevalence of invasive ventilation among transferred patients.

The risk of interhospital transfer has been investigated to some extent in observational studies, albeit with conflicting results. A Swedish register-based study of 2,912 capacity-transferred ICU patients before the pandemic found that transportation was associated with a lower risk of death within 90 days (odds ratio 0.71, 95% CI: 0.65–0.79) (20). Conversely, another Swedish study including 11,176 ICU patients showed a higher risk of 30-day mortality after capacity transfers (odds ratio 1.25, 95% CI: 1.06–1.49) and clinical transfers (odds ratio 1.17, 95% CI: 1.02–1.36) (21). However, the reference consisted of repatriated patients. While we excluded such patients in our study, other studies have confirmed that clinical transfer to a higher level of care is associated with better patient outcomes (22, 23). A French cohort study of 18,348 COVID-19 patients in the ICU found that transferred patients had a lower mortality rate than non-transferred patients, concluding that this might be due to a rigorous selection process of patients eligible for transfer (15). However, the study only included patients from the first wave of the pandemic. This finding resembles ours, where the results were driven by lower mortality in IHT patients during the first COVID wave. A retrospective cohort study including 5,207 patients mostly with SARS-CoV-2 during

wave 3 of the pandemic in Australia found no association between IHT and mortality (12). Combining the findings of the present study with the previous literature makes it reasonable to argue that IHT of ICU patients does not appear to increase mortality. Nevertheless, there may be other drawbacks to IHTs, such as hospital-acquired infections, discontinued care, information gaps or patients being intubated to ensure safe transport, which may prolong the hospital stay (24, 25).

The observed absence of increased mortality risk associated with the transfer may be explained by the fact that patients with recovery potential were carefully selected to be stable enough to tolerate transport safely. This aligns with the results from the above-mentioned French study (15). Furthermore, the technical difficulties associated with transporting patients with high-flow oxygen therapy with high oxygen fractions most likely contributed to the decision to avoid such transfers, which was reflected in our study where mechanical ventilation was more common in the transferred group.

The main methodological strengths of this study were the comprehensive data collection conducted by dedicated researchers during the three pandemic waves and validated by independent researchers, the low proportion of missing data, and the adjustment for known confounders in the analyses. Among the main weaknesses are the single-centre design and the non-randomised design. There may be a selection bias in the study, with patients on invasive ventilation and therefore with a secured airway and having limitations of care to a lesser extent, such as do not resuscitate orders, in the transferred group. This might explain the lower OR for mortality in the adjusted analysis and also the longer ICU LOS, as the treatments were not discontinued.

Assessing illness during transport and comparing different patient groups presents several challenges. Information about the severity of illness immediately before transport, which might be more appropriate to include in the analyses than the severity of illness at ICU admission, was not readily available. We did not find sufficient and reliable data to analyse this in our cohort. Furthermore, we have not investigated patients' functional status after ICU discharge, which is of high importance for evaluating surviving patients' wellbeing.

Differences in mortality between countries may depend on variations in healthcare structure and the degree of burden that the country and the healthcare organisation experienced during the pandemic. Well-established routines for transport, availability of advanced medical transport equipment, and access to the same electronic patient data management systems for transferring and admitting centres may also influence the safety of transport. However, taken together, the findings of this study may be somewhat generalisable to countries with similar demographics, pandemic situations and healthcare to X. Future studies should focus on whether certain patient characteristics are predictive of safe transfers, and should study the effects of transfers on surviving patients' ability to recover. Furthermore, it is important to explore various types of complications related to IHT and long-term outcomes to identify factors that may influence treatment outcomes and thereby improve care.

CONCLUSIONS

This study indicates that interhospital transfer due to capacity constraints among patients with critical COVID-19 was associated with lower mortality but an extended length of ICU stay, probably due to the need for invasive ventilation among transferred patients and not

the transfer per se. Suitability for transfer is probably associated with lower mortality, and residual confounding cannot be excluded.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualisation, methodology, design: X, X, X, X, X, X. Analysis: X, X and X. Writing of the original draft: X, X, X. Review and editing: All authors. Final approval of submitted manuscript: All authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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Figure 1

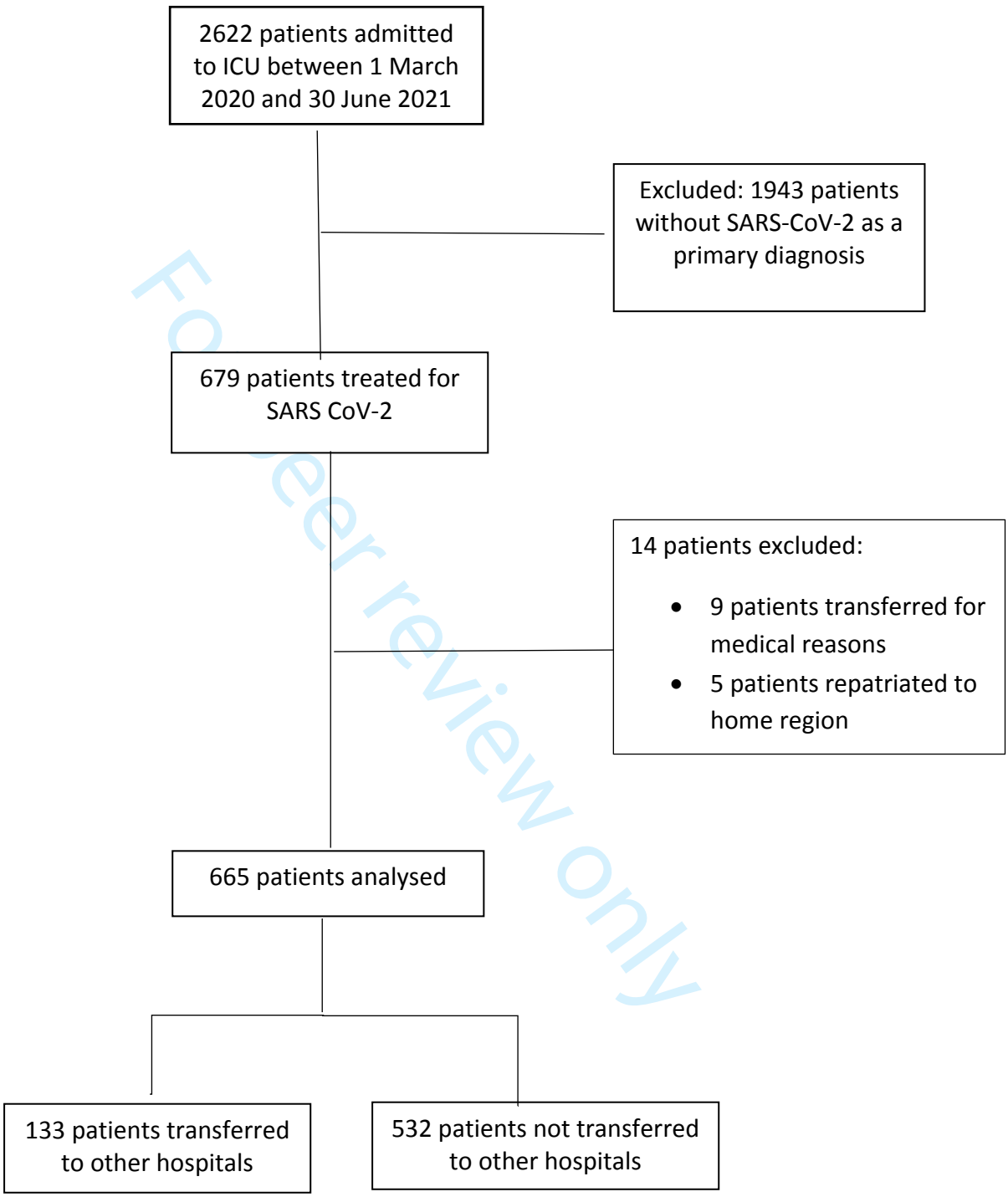


Table 1. Characteristics of patients admitted to an ICU for SARS-CoV-2

	All patients	Non-IHT patients	IHT patients	p-value
Total number (%)	665	532 (80)	133 (20)	
Age, median (IQR)	64 (55–72)	64 (55–72)	65 (57–71)	ns
Sex, n (%)				ns
Men	479 (72)	376 (71)	103 (77.4)	
Women	186 (28)	156 (29)	30 (23)	
BMI, n (%)				ns
>30	253(38)	202 (38)	51 (38)	
<30	406 (62)	324 (61)	82 (62)	
SAPS 3, mean ± SD		58 (47–67)	57 (49–65)	ns
CCI category, n (%)				ns
0	248 (37)	197 (37)	51 (38)	
1	250 (38)	198 (37)	52 (39)	
≥2	167 (25)	137 (26)	30 (23)	
Invasive ventilation, n (%)				<0.001*
Yes	344 (52)	213 (40)	131 (98)	
No	321 (48)	319 (60)	2 (2)	
Limitations on life-sustaining treatments, n (%)				0.001*
Yes	83 (12)	78 (15)	5 (4)	
No	582 (88)	454 (85)	128 (96)	
COVID-19 period, n (%)				ns
Wave 1	265 (40)	218 (41)	47 (35)	
Waves 2–3	400 (60)	314(59)	86 (65)	

Table 1. Characteristics of patients admitted to an ICU for SARS-CoV-2

Abbreviations: BMI: body mass index; SAPS 3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index score; SD: Standard deviation; ns=no statistically significant differences, *p<0.05 statistically significant differences

Table 2. Risk of death 30 days and 90 days after interhospital transfer among critically ill patients with SARS-CoV-2 presented as hazard ratios with 95% CI (Non-IHT as reference)

	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
Variables	No (%)	30 days No (%)	90 days No (%)	**Unadjusted model** Hazard ratios 95% CI	**Adjusted model** Hazard ratios 95% CI	**Unadjusted model** Hazard ratios 95% CI	**Adjusted model** Hazard ratios 95% CI
All patients							
Non-IHT	532 (80)	136 (26)	157 (30)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	133 (20)	25 (19)	34 (26)	0.66 (0.43–1.02)	0.47 (0.30–0.76) *	0.79 (0.54–1.14)	0.52 (0.34–0.78) *

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (0, 1, >2), mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1/waves 2–3). *Statistically significant differences between groups, p<0.05

Abbreviations: IHT: inter-hospital transport; CI: confidence interval.

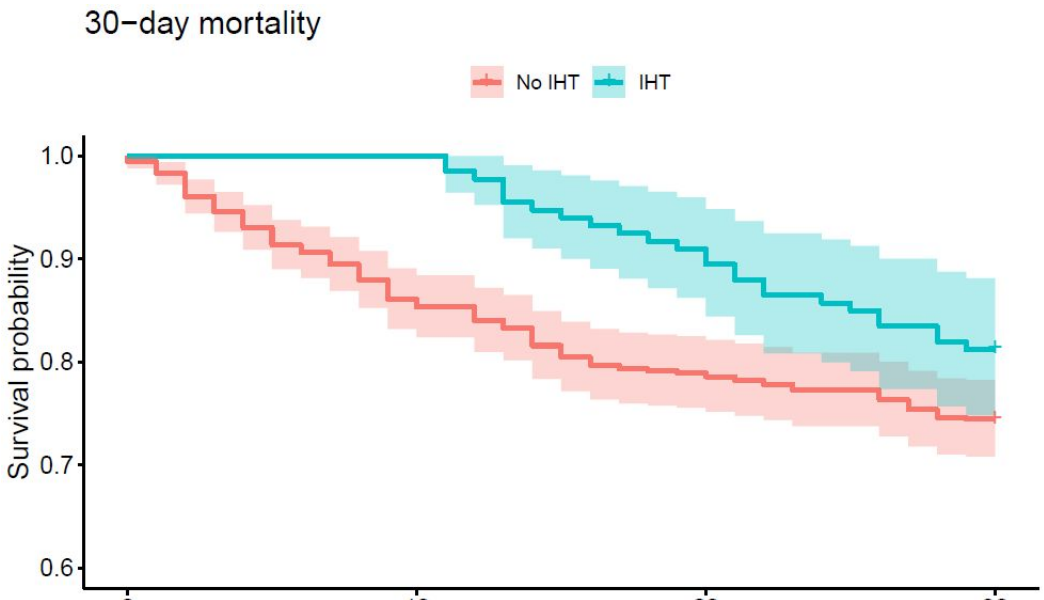
Table 3. Sensitivity analyses regarding the risk of 30-day and 90-day mortality after interhospital transfe by length of ICU stay presented as hazard ratios with 95% CI (Non-IHT as reference

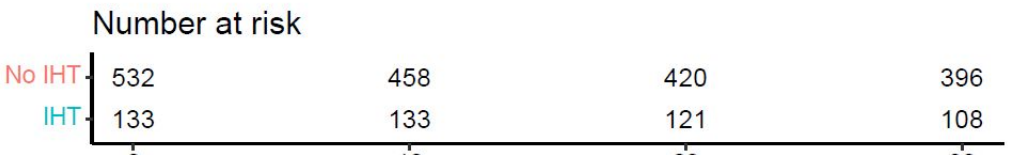
Risk of death for IHT by length of ICU stay							
	Exposure	Mortality		**30-day mortality HR with 95% CI**		**90-day mortality HR with 95% CI**	
ICU LOS				Unadjusted	Adjusted	Unadjusted	Adjusted
>6 days							
Non-IHT	241 (65)	70 (29)	83 (34)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	127 (35)	25 (20)	34 (27)	0.62 (0.39–0.97)*	0.42 (0.26–0.68) *	0.70 (0.47–1.05)	0.45 (0.29–0.69)*
>8 days							
Non-IHT	187	57(31)	69 (37)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	118	24(20)	33 (28)	0.61 (0.38–0.98)*	0.40 (0.24–0.67)*	0.69 (0.45–1.04)	0.43 (0.28–0.67)*
>10 days							
Non-IHT	161	49 (30)	61 (38)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	106	22 (21)	31 (29)	0.63 (0.38–1.05)	0.46 (0.27–0.78)*	0.71 (0.46–1.09)	0.49 (0.31–0.77)*
>12 days							
Non-IHT	147 (60)	44 (30)	55 (37)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	94 (40)	21 (22)	30 (32)	0.71 (0.42–1.19)	0.48 (0.28–0.85)*	0.80 (0.51–1.25)	0.53 (0.33–0.85)*

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (0, 1, >2), mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1 or waves 2/3). *Statistically significant differences between groups, p<0.05

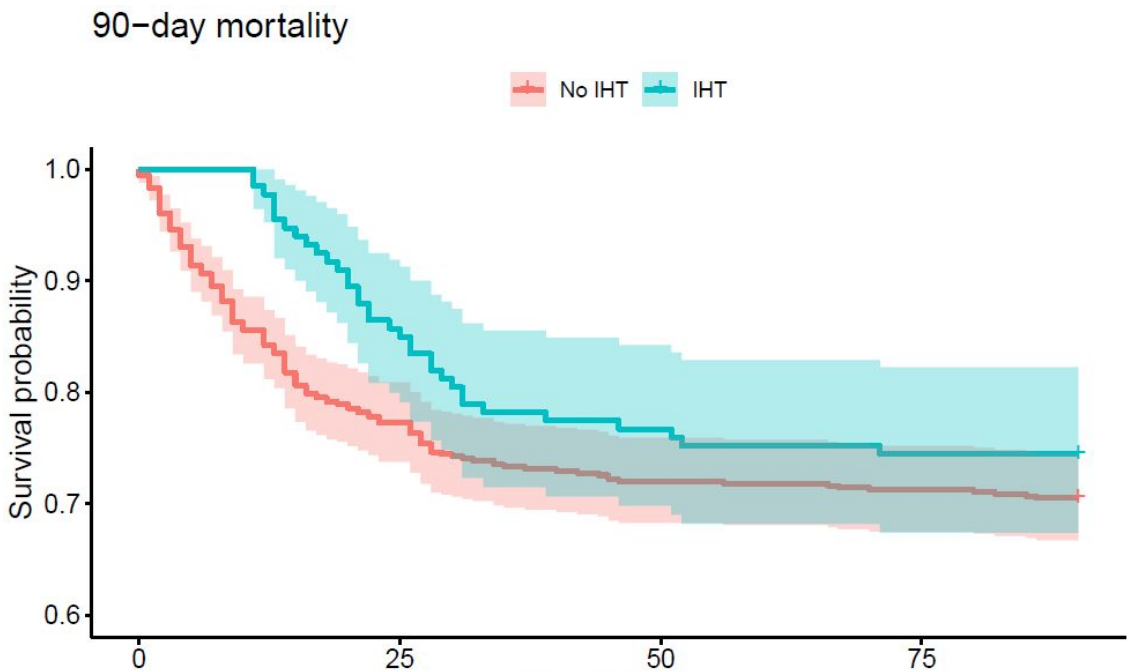
Abbreviations: LOS: length of stay; ICU: intensive care unit; IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

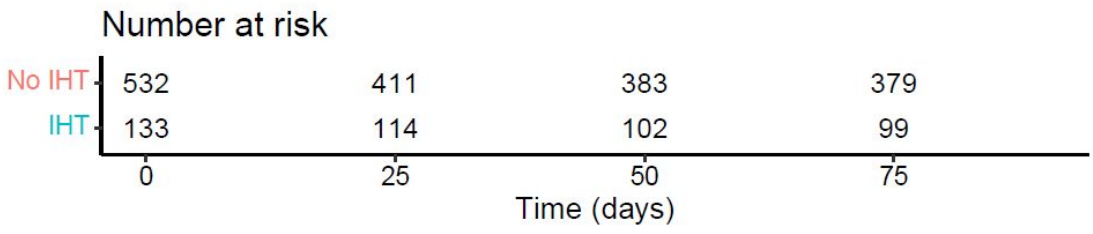
FIGURES



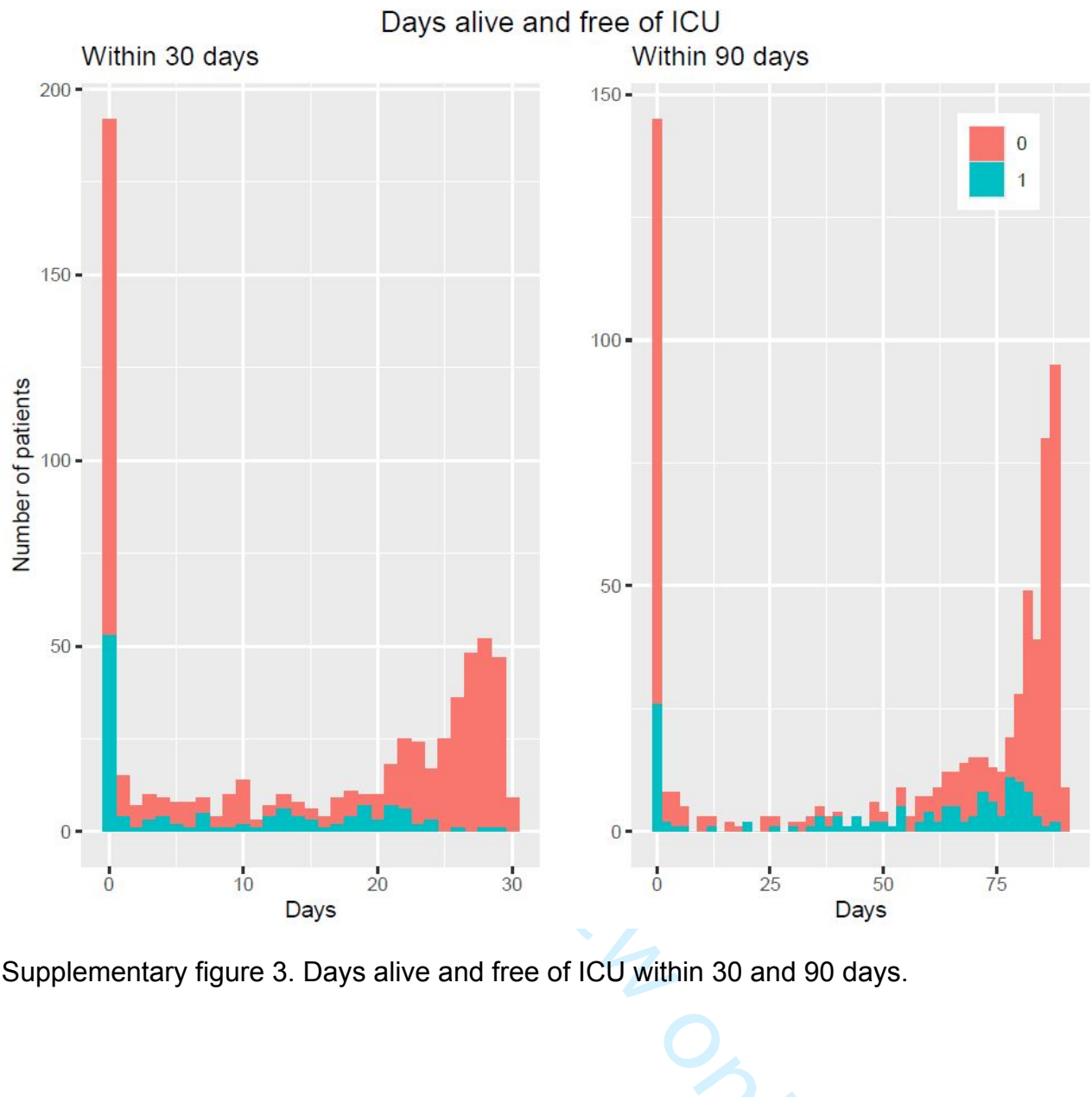


Supplementary figure 1. Kaplan-Meier curve showing survival to day 30 from ICU admission for patients with SARS-CoV-2 infection in Sweden between 1 March 2020 and 30 June 2021.

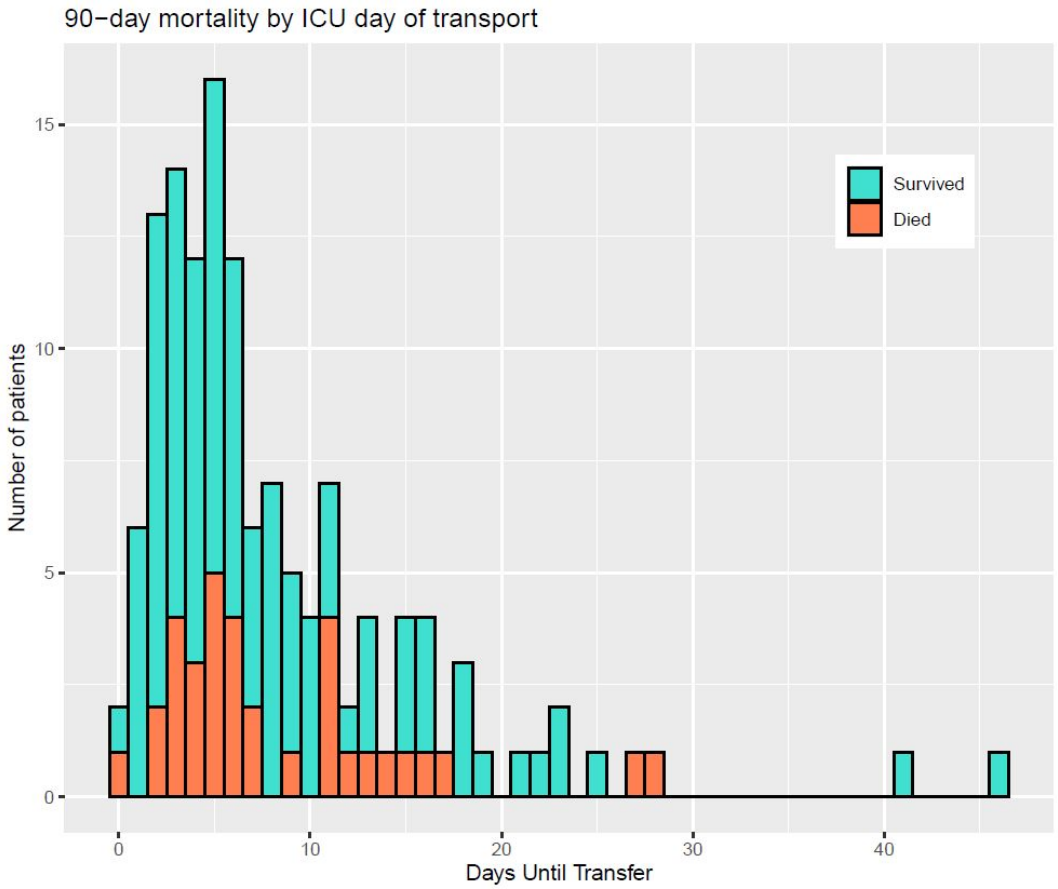




Supplementary figure 2. Kaplan-Meier curve showing survival to day 90 from ICU admission for patients with SARS-CoV-2 infection in Sweden between 1 March 2020 and 30 June 2021.



Supplementary figure 3. Days alive and free of ICU within 30 and 90 days.



Supplementary Figure 4. Patient distribution of 90 days mortality by ICU day of transfer

For the group without mechanical ventilation (total 321, 319 without IHT and two with IHT), neither of the two patients with exposure to IHT died within either 30 or 90 days compared to the 66 patients (21%) in the group without mechanical ventilation in the group not exposed to IHT. Due to the small number of patients and no event in the group without mechanical ventilation and IHT, the analyses were neither of interest nor statistically appropriate.

When analysing only the subgroup of patients with mechanical ventilation (total 344, 213 without IHT and 131 with IHT), the results showed a reduced risk of death in both the univariate model, HR 0.51 (95% CI 0.32–0.81) for 30-day mortality and HR 0.60 (95% CI 0.40–0.89) for 90-day mortality, and the multivariate model, HR 0.40 (95% CI 0.25–0.65) for 30-day mortality and HR 0.45 (95% CI 0.30–0.68) for 90-day mortality.

For the group with treatment limitations (total 83, 78 without IHT and five with IHT), three patients (60 %) with exposure to IHT died within 30 and 90 days compared to the 55 (66%) and 58 (70%) with no exposure to IHT in 30 and 90 days, respectively. Even though the percentage was about the same in the two groups, the analysis was not carried out due to the small number of patients exposed to IHT with treatment limitations. For the patient group without treatment limitations (total 582, 454 without IHT and 128 with IHT), the results were the same as in the original models, showing no difference between patients without exposure to IHT compared to patients with exposure in the univariate model, HR 0.92 (0.58-1.48) for 30-day mortality and HR 1.08 (95% CI 0.72–1.60) for 90-day mortality, and a difference in the multivariate model, HR 0.38 (95% CI 0.23–0.62) for 30-day mortality and HR 0.45 (95% CI 0.29–0.68) for 90-day mortality.

For the group of patients treated during the first COVID-19 wave (total 265, 218 without IHT and 47 with IHT), the results showed a reduced risk of death in the univariate analyses for 30-day mortality, HR 0.26 (95% CI 0.10–0.73). For the univariate analyses for 90-day mortality and the multivariate analyses for both the 30- and 90-day mortality, the results were unchanged, HR 0.44 (95% CI 0.20–0.96), HR 0.24 (95% CI 0.08-0.66) and HR 0.38 (95% CI 0.17–0.85). For the group treated during COVID waves 2 and 3 (total of 400, 314 without IHT and 86 with IHT), the results also differed from the original multivariate models. In this subgroup, there was still no difference between patients with and without exposure to IHT in the univariate models, with HR 0.95 (95% CI 0.58 to 1.54) for 30-day mortality and HR 1.01 (95% CI 0.65–1.54) for 90-day mortality. However, contrary to the findings in the whole cohort, there was no longer a difference in the associated risk of 30- and 90-day mortality in the multivariate models, HR 0.68 (95% CI 0.38-1.18) and HR 0.63 (95% CI 0.38-1.04)

Supplementary Table 6. Characteristics of mechanically ventilated patients admitted to an ICU for SARS-CoV-2 (non-invasive ventilated patients were excluded)

	All patients	Non-IHT patients	IHT patients	p-value
Total number (%)	344	213	131	
Age, median (IQR)	64 (55–71)	64 (55–71)	65 (57–72)	ns
Sex, n (%)				ns
Men	258 (75)	157 (74)	101 (77)	
Women	86 (25)	56 (26)	30 (23)	
BMI, n (%)	(n=341)	(n=210)		ns
>30	139 (41)	89 (42)	50 (38)	
<30	202 (59)	121 (58)	81 (62)	
SAPS 3, median (IQR)	57 (53–63)	57 (53–63)	57 (53–63)	ns
CCI category, n (%)				ns
0	132 (38)	82 (39)	50 (38)	
1	133 (39)	81 (38)	52 (40)	
≥2	70 (23)	50 (23)	29 (22)	
Limitations on life-sustaining treatments, n (%)				ns
Yes	16 (5)	11 (5)	5 (4)	
No	328 (95)	202 (95)	126 (96)	
COVID-19 period, n (%)				0.003*
Wave 1	160 (47)	113 (53)	47 (36)	
Waves 2–3	184 (53)	100 (47)	84 (64)	

Abbreviations: BMI: body mass index; SAPS 3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index score; SD: standard deviation; ns=no statistically significant differences, *p<0.05 statistically significant differences

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Interhospital transports and mortality in patients with critical COVID-19: a single-centre cohort study

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ABSTRACT

Objectives

This study aimed to compare mortality rates and length of hospital stay between patients with critical COVID-19 transferred to another hospital due to capacity constraints and those who remained at their initial admission hospital.

Design

Single-centre cohort study

Setting and participants

Six hundred and sixty-five patients treated for SARS-CoV-2 at two intensive care units (ICU) in Stockholm, Sweden from 1 March 2020 to 30 June 2021. Data on interhospital transfers were retrieved from medical records and patient data management systems according to pre-defined protocols.

Main outcome measures

The outcomes were 30- and 90-day mortality, days alive and out of ICU. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazard models with adjustments for age, sex, body mass index, severity of illness, comorbidity, invasive ventilation, treatment limitations and pandemic waves.

Results

Of 665 patients, 133 (20%) were transferred to another hospital. The mortality rate for transferred patients compared to non-transferred patients at 30 days was 19% versus 26%

(p=0.13) and at 90 days 26% versus 30% (p = 0.43). In the adjusted Cox regression analysis, interhospital transfer was associated with a lower mortality risk at 30 days (HR 0.47, 95% CI: 0.30–0.76) and 90 days (HR 0.52, 95% CI: 0.34–0.79). However, the number of days alive and out of ICU was significantly lower for the IHT group at 30 and 90 days.

Conclusion

In our study, interhospital transfer due to capacity constraints among critically ill COVID-19 patients was not associated with a higher mortality risk. The suitability for transfer was likely associated with lower mortality, although residual confounding cannot be ruled out. The requirement for invasive ventilation among transferred patients might account for the extended length of ICU stay, rather than the transfer itself. However, the difficulty in studying this issue lies in the fact that while patients are likely exposed to risks during transfer, they are simultaneously the patients stable enough to be transported.

Strengths and limitations of this study

- The strengths are the comprehensive data collection conducted by dedicated researchers during the three pandemic waves and validated by independent researchers.
- The low proportion of missing data, and the adjustment for known confounders in the analyses.
- The main weakness is the single-centre non-randomised design.
- There may be a risk of selection bias in the study since it is likely that respiratory – and hemodynamic-stable patients with recovery potential were selected for transport.

- Information about the severity of illness immediately before transport was not readily available in our cohort.

BACKGROUND

Transports of critically ill patients between intensive care units (ICUs) across hospitals are relatively common. The primary reasons include the need to transfer to a hospital with specialised competence, as well as capacity constraints at the transferring hospital [1-3]. Regardless of the reason for the transport, studies have shown that patient transfers entail direct risks related to the transport itself and can be linked to delayed diagnostics or treatments [1 4-8]. In the years before the COVID-19 pandemic, around 600 ICU patients (1.8%) were transported between hospitals in Sweden each year due to resource shortages at the sending ICU. However, during the pandemic, the influx of patients requiring ICU treatment significantly increased interhospital transfers (IHTs) to 3.5% [9].

Studies investigating the risk of IHT during the COVID-19 pandemic have shown conflicting results. Some studies indicate that IHT is not associated with an increased mortality risk [2 10-13] or may even be associated with a lower risk of death [14], whereas others have shown that IHT is associated with a longer duration of mechanical ventilation [10-12], ICU stay [11] and length of hospital stay [2 11 12]. None of these studies were randomised controlled trials, and many were limited by a small sample size [2 10 13]. Despite the large increase in ICU beds in Sweden during the pandemic, a substantial proportion of critically ill patients were transferred between hospitals. To the best of our knowledge, no study has so far studied the influence of IHTs on patient outcomes during the COVID-19 pandemic in Sweden. Therefore, we aimed to compare mortality rates and length of hospital stay between patients transferred to

another hospital due to capacity constraints and those who remained at their initial admission hospital.

METHODS

Study design

This study included all adult patients (age ≥18 years) with confirmed SARS-CoV-2, as verified by polymerase chain reaction test, requiring intensive care at Södersjukhuset, Sweden, between 1 March 2020 and 30 June 2021. The hospital is a secondary referral centre, serving a diverse range of medical and surgical patients in Stockholm, a city with 2.5 million inhabitants. The hospital has a total capacity of 600 beds and houses a large emergency department with a continuous inflow of acutely ill patients. Healthcare in Sweden is predominantly funded by taxes, ensuring access to medical services for all citizens. Normally, there are 18 beds dedicated to intensive care. However, during the COVID-19 pandemic, the ICUs expanded to accommodate a total of 60 ICU beds. The study was approved by the Swedish Ethical Review Authority (Dnr: 2023-01778-01-380347, amendment 2023-01778-01), and the requirement for written informed consent from patients was waived. The reporting of the study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15].

Cohort

All adult patients with a SARS-CoV-2 diagnosis and initial admission at the study hospital's ICU were eligible for inclusion in the study. Patients first admitted to other ICUs and subsequently transferred to the study hospital were excluded. Additionally, patients transferred due to reasons other than capacity constraints, such as repatriation (return to a local ICU near the patient's home) and clinical transfers (requiring specialized care not available at the admitting hospital) were excluded from the study.

Patients were identified using the patient data management system. Clinical data were automatically and manually extracted from medical records and the patient data management system using a pre-defined data collection protocol to ensure consistency and uniformity of the data collection. Cross-validation of data from randomly selected patients was performed separately by two independent researchers.

Exposure

The exposure was Interhospital Transfer (IHT), specifically defined as the transfer of patients from the Intensive Care Unit (ICU) at the index hospital to another hospital's ICU due to capacity constraints. These constraints typically involve a shortage of staffed ICU beds at the referring hospital, necessitating the transfer of patients to ensure they receive the critical care they need.

The interhospital transfers were conducted in accordance with the transport recommendations provided by the Swedish Society for Anaesthesia and Intensive Care. These guidelines ensure that transfers are carried out safely and efficiently, minimising risks to the patient during transport. The guidelines cover various aspects, such as patient stability before the transfer, necessary medical equipment during the transfer, and the qualifications of the medical personnel accompanying the patient. The transfers were crucial for managing ICU capacity and ensuring that patients continue to receive appropriate care without delay [16]. The selection of patients for transfer was commonly carried out in consultation with the admitting ICU. The decision was based on the patient's physiological status to ensure safe transport and the receiving hospital's capacity to provide the required care. This process did not adhere to a standardized protocol or guideline; rather, it relied on the clinical judgment of senior physicians, who made joint decisions about which patient was most suitable for

transfer, based on various clinical factors and the urgency of the situation. The decision-making process involved assessing the patient's condition, stability, and the potential risks and benefits of transfer aiming to ensure that the patient most in need of ICU care at another facility was selected for transfer, taking into consideration the overall capacity and resources of both the referring and receiving hospitals. The lack of a standardized protocol meant that decisions were tailored to individual cases relying of clinical expertise and teamwork in managing ICU capacity and patient care.

The transport was prepared according to local routines, and handover was reported by telephone. ICU patients in Stockholm are commonly transported between hospitals using a mobile intensive care unit (MICU). A MICU is staffed with one ambulance nurse, one paramedic and one physician from the departing intensive care unit. The MICU transporter is more spacious than a standard ambulance and is equipped with continuous electrocardiography monitoring, invasive hemodynamic monitoring and advanced ventilatory support. Information about the date, time and reasons for transfer was obtained from the patient's medical records and the patient data management system.

Outcomes

The outcomes were mortality at days 30 and 90 from ICU admission and days alive and out of ICU. The length of ICU stay was measured from the date of ICU admission to the date of discharge from the ICU at Södersjukhuset or the admitting hospital.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables are expressed as numbers and proportions (percentages). The distribution of continuous variables was tested with the Shapiro-Wilk test. Differences between groups were analysed using the Mann-Whitney U test and the Chi^2 test for continuous and categorical variables, respectively.

In the survival analyses, patients were followed up from the date of ICU admission until the date of death or until 30 and 90 days had passed since admission. Kaplan–Meier curves were used to estimate the cumulative risk of death, and the log-rank test was employed to compare patients with exposure to IHT versus those without IHT. Cox proportional hazards regression was used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) for death within 30 and 90 days from ICU admission. Multivariate models were adjusted for age (continuous), sex (male/female), body mass index (<30/≥30 kg/m^2), Simplified Acute Physiology Score III (SAPS III) (>50/50–59/≥60), Charlson Comorbidity Index (categorised as 0/1/2) [17], invasive mechanical ventilation (yes/no), treatment limitations (yes/no), COVID waves (first wave, March to September 2020 versus second and third waves, October 2020 to January 2021 and February to June 2021 [18]) and IHT (yes/no). Both crude and multivariable models were investigated with no IHT as the reference group. Scaled Schoenfeld residuals were regressed against survival time to assess the proportional hazard assumptions, and Martingale residual plots, together with the Grambsch-Therneau test, were used to assess evidence of non-linearity. Variance inflation factors were used when investigating multicollinearity. All variables were complete except for SAPS and BMI which were missing for 105 and 6 patients, respectively. This was handled by a separate category for patients with missing values.

Since the proportional hazards assumption in the Cox regression was not met, indicating that the effect of the variables could vary over time, we performed sensitivity analyses on subgroups of patients based on length of ICU stay (more than 6, 8, 10 and 12 days), COVID waves, mechanical ventilation and treatment limitations. Comparisons of days alive free from ICU were conducted using the Mann-Whitney U test and presented as medians with interquartile ranges (IQRs).

A two-sided p-value less than 0.05 was considered statistically significant. The analysis followed a predefined protocol and was conducted using the IBM SPSS Statistics version 29 statistical software and R version 4.3.3 (R Core, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). All analyses were discussed and confirmed with an experienced biostatistician.

RESULTS

Patient cohort

Of 2622 critically ill patients admitted to the two ICUs during the study period, 674 had a confirmed SARS-CoV-2 diagnosis. Nine patients were transported to other hospitals for tertiary care (e.g. ECMO) and five patients had been transferred to the study hospital from other hospitals/regions. In total, 665 SARS-CoV-2 patients were included in the study, of which 133 (20%) underwent interhospital transports due to capacity constraints (Figure 1). All patients (n=133) were transported to a hospital within a 30-kilometer radius or maximum of 30 minutes.

The median age of included patients was 64 years, and most were men (72%). Patients who were transferred were more often on mechanical ventilation (98%) compared with the non-transferred patients (40%), and fewer had limitations in terms of life-sustaining treatment (4% versus 15%). Otherwise, the groups were balanced regarding patient and clinical characteristics (Table 1). The median day of IHT from admission was 6 (IQR: 3–11).

Interhospital capacity transfer and mortality

Analyses of IHT and mortality in patients with critical COVID-19 are shown in Table 2. Mortality rates did not differ between groups at either 30 days (19% vs. 26%, p = 0.13) or 90 days (26% vs. 30%, p = 0.43). This was consistent across the log-rank test for survival for 30 days (Figure 2, p = 0.06) and 90 days (Figure 3, p = 0.2), as well as the HR of the univariate Cox regression of 0.66 (95% CI: 0.43–1.02) for 30-day mortality and 0.79 (95% CI: 0.54–1.14) for 90-day mortality. When the exposure of IHT was analysed in the multivariate model, it

was associated with a lower risk of mortality for both 30 days (HR 0.47, 95% CI: 0.30–0.76) and 90 days (HR 0.52, 95% CI: 0.34–0.79) (Table 2).

As the assumptions of proportional hazards were violated when scaled Schoenfeld residuals were regressed against survival time (p <0.001 for the multivariate model for 30- and 90-day mortality), sensitivity analyses were performed. When splitting the time and analysing by different lengths of stay (LOS) at the ICU, the assumptions were fulfilled for patients with a LOS of eight days and above (p = 0.14 for 30-day mortality and p = 0.09 for 90-day mortality). The results did not differ from the original models except for IHT being associated with lower 30-day mortality, including in the univariate analyses for patients with an ICU LOS of more than six and eight days (Table 3). Schoenfeld residuals indicated violations of proportional hazard assumptions, including for the covariates of mechanical ventilation, treatment limitations and COVID-19 wave in the multivariate models for 30 and 90 days. This issue was addressed by examining the various categories within these variables as subgroups. The reason for the violation of the variables of mechanical ventilation and treatment limitations was a small number of patients/events in the groups of patients without mechanical ventilation exposed to IHT and the group with treatment limitations exposed to IHT. When analysing the subgroup of only mechanically ventilated patients, the results changed in the univariate models, showing a lower risk of mortality for 30 days (19.3% versus 32.9%, p=0.008) and 90 days (26.0% versus 38.0%, p=0.029) in the IHT group compared to the non-IHT group. In the multivariate models, the decrease in mortality for the IHT group at 30 and 90 days remained unchanged. Excluding patients with treatment limitations did not change the results.

Interhospital capacity transfer and mortality by COVID-19 wave

For the group of patients treated during the first COVID-19 wave, the univariate analyses for 30-day mortality showed a reduced risk of death, with a hazard ratio (HR) of 0.26 (95% CI: 0.10–0.73). The univariate analyses for 90-day mortality and the multivariate analyses for both 30- and 90-day mortality remained consistent, with HRs of 0.44 (95% CI: 0.20–0.96), 0.24 (95% CI: 0.08–0.66), and 0.38 (95% CI: 0.17–0.85), respectively (Table 4).

For the group treated during the second and third COVID-19 waves, the results differed from the original multivariate models. In this subgroup, there was still no significant difference between patients with and without IHT in the univariate models, with HRs of 0.95 (95% CI: 0.58–1.54) for 30-day mortality and 1.01 (95% CI: 0.65–1.54) for 90-day mortality. However, unlike the findings in the whole cohort, there was no longer a significant difference in the associated risk of 30- and 90-day mortality in the multivariate models, with HRs of 0.68 (95% CI: 0.38–1.18) and 0.63 (95% CI: 0.38–1.04), respectively (Table 4).

More details regarding the subgroup analyses can be found in Supplementary files 1-3.

Interhospital transfer and days alive free of ICU

Compared with non-IHT patients, IHT patients had in median fewer days alive and free from the ICU at 30 days (5, IQR: 0–18 versus 22, IQR: 0–27, p<0.001) and 90 days (64, IQR: 27–78 versus 81, IQR: 6–87, p=0.86) respectively (Figure 4). However, for mechanically ventilated patients, there were no statistically significant median differences between the groups at 30 days (5, IQR: 0–18 versus 2, IQR: 0–16, p=0.31) or 90 days (63, IQR: 24–78 versus 60, IQR: 0–75, p=0.14).

DISCUSSION

In this study, transfers solely due to capacity constraints during the COVID-19 pandemic were not associated with a higher risk of 30- and 90-day mortality among patients with critical COVID-19. Our results indicated that such transfers may even be associated with a lower mortality risk, especially for mechanically ventilated patients. Interhospital transfer was associated with a longer ICU LOS compared with patients who remained in the admitting ICU. This was probably explained by the higher prevalence of invasive ventilation among transferred patients.

The risk of interhospital transfer has been investigated to some extent in observational studies, albeit with conflicting results. A Swedish register-based study of 2,912 capacity-transferred ICU patients before the pandemic found that transportation was associated with a lower risk of death within 90 days (odds ratio 0.71, 95% CI: 0.65–0.79) [19]. Conversely, another Swedish study including 11,176 ICU patients showed a higher risk of 30-day mortality after capacity transfers (odds ratio 1.25, 95% CI: 1.06–1.49) and clinical transfers (odds ratio 1.17, 95% CI: 1.02–1.36) [20]. However, the reference consisted of repatriated patients. While we excluded such patients in our study, other studies have confirmed that clinical transfer to a higher level of care is associated with better patient outcomes [21 22]. A French cohort study of 18,348 COVID-19 patients in the ICU found that transferred patients had a lower mortality rate than non-transferred patients, concluding that this might be due to a rigorous selection process of patients eligible for transfer [14]. However, the study only included patients from the first wave of the pandemic. This finding resembles ours, where the results were driven by lower mortality in IHT patients during the first COVID wave. A retrospective cohort study including 5,207 patients mostly with SARS-CoV-2 during wave 3 of the pandemic in Australia found no association between IHT and mortality [11]. The difference

in outcomes between the pandemic waves may be attributed to changes in healthcare conditions among patients and the accumulated experience in managing the disease. Although capacity constraints remained high during the pandemic waves, the outcomes improved due to the learning curve in treating COVID-19 patients and the implementation of standardized treatments.

Combining the findings of the present study with the previous literature makes it reasonable to argue that IHT of ICU patients does not appear to increase mortality. Nevertheless, there may be other drawbacks to IHTs, such as hospital-acquired infections, discontinued care, information gaps or patients being intubated to ensure safe transport, which may prolong the hospital stay [23 24].

The observed absence of increased mortality risk associated with the transfer may be explained by the fact that patients with recovery potential were carefully selected to be stable enough to tolerate transport safely. This aligns with the results from the above-mentioned French study [14]. Furthermore, the technical difficulties associated with transporting patients with high-flow oxygen therapy with high oxygen fractions most likely contributed to the decision to avoid such transfers, which was reflected in our study where mechanical ventilation was more common in the transferred group.

The main methodological strengths of this study were the comprehensive data collection conducted by dedicated researchers during the three pandemic waves and validated by independent researchers, the low proportion of missing data, and the adjustment for known confounders in the analyses. Among the main weaknesses are the single-centre design and

the non-randomised design. There may be a selection bias in the study, with patients on invasive ventilation and therefore with a secured airway and having limitations of care to a lesser extent, such as do not resuscitate orders, in the transferred group. This difference might explain the lower OR for mortality in the adjusted analysis and also the longer ICU LOS, as the treatments were not discontinued. In this study, we selected mortality and days alive and out of the ICU as one of the outcome measures. However, we acknowledge that organ support-free days could have been another valuable parameter to assess the impact of transfers. This alternative measure could provide additional insights into the safety of interhospital transfers. Assessing illness during transport and comparing different patient groups presents several challenges. Information about the severity of illness immediately before transport, which might be more appropriate to include in the analyses than the severity of illness at ICU admission, was not readily available. We did not find sufficient and reliable data to analyse this in our cohort. Furthermore, we used SAPS III to assess illness severity instead of the more commonly used systems like APACHE II or IV. SAPS III is the standard scoring system for intensive care patients in Sweden and is utilised for reporting to the Swedish Intensive Care Register (SIR), ensuring consistency and accuracy within the national context. However, this choice may limit the direct comparability of our results with studies using other scoring systems. Fourteen per cent of SAPS data were missing. The missingness was primarily due to manual documentation processes during the pandemic, leading to a gap at one of the ICUs. This gap was likely caused by work-related issues rather than patient-related factors. Patients across the two ICUs were similar in clinical characteristics and diagnoses, and all other variables were complete, supporting the assumption that the missing data were random. We also conducted a sensitivity analysis

with complete cases and the results remained unchanged. Another issue was that lifestyle factors such as smoking, physical activity, and alcohol consumption, as well as socio-economic variables like deprivation, education, and employment status, were not available in our dataset. As such, we were unable to adjust for these variables in the analysis. Furthermore, we have not investigated patients' functional status after ICU discharge, which is of high importance for evaluating surviving patients' well-being.

Differences in mortality between countries may depend on variations in healthcare structure and the degree of burden that the country and the healthcare organisation experienced during the pandemic. Well-established routines for transport, availability of advanced medical transport equipment, and access to the same electronic patient data management systems for transferring and admitting centres may also influence the safety of transport. The findings of this study may be somewhat representative to countries with comparable population structures, healthcare systems, and pandemic responses. The use of standardised healthcare protocols ensures consistency in patient care and treatment, which can make the results of this study applicable to other regions facing similar challenges. Future studies should focus on whether certain patient characteristics are predictive of safe transfers and should study the effects of transfers on surviving patients' ability to recover. Furthermore, it is important to explore various types of complications related to IHT and long-term outcomes to identify factors that may influence treatment outcomes and thereby improve care.

CONCLUSIONS

In our study interhospital transfer due to capacity constraints among critically ill COVID-19 patients was not associated with a higher mortality risk. The suitability for transfer was likely

associated with lower mortality, although residual confounding cannot be ruled out. The requirement for invasive ventilation among transferred patients might account for the extended length of ICU stay, rather than the transfer itself. However, the difficulty in studying this issue lies in the fact that while patients are likely exposed to risks during transfer, they are simultaneously the patients stable enough to be transported.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

KB: Conceptualisation, methodology, design, analysis, writing the original draft, review and editing. LTA: Conceptualisation, methodology, design, writing the original draft, review and editing. PS: conceptualisation, methodology, design, review and editing. MC: Conceptualisation, methodology, design, review and editing. SJ: conceptualisation, methodology, design, analysis, review and editing. EJA: conceptualisation, methodology,

design, review and editing. AS: conceptualisation, methodology, design, analysis, writing the original draft, review and editing. AS: are responsible for the overall content as guarantor.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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Table 1. Characteristics of patients admitted to an ICU for SARS-CoV-2

	All patients	Non-IHT patients	IHT patients	p-value
Total number (%)	665	532 (80)	133 (20)	
Age, median (IQR)	64 (55–72)	64 (55–72)	65 (57–71)	ns
Sex, n (%)				ns
Men	479 (72)	376 (71)	103 (77.4)	
Women	186 (28)	156 (29)	30 (23)	
BMI, n (%)				ns
>30	253(38)	202 (38)	51 (38)	
<30	406 (62)	324 (61)	82 (62)	
SAPS 3, mean ± SD		58 (47–67)	57 (49–65)	ns
CCI category, n (%)				ns
0	248 (37)	197 (37)	51 (38)	
1	250 (38)	198 (37)	52 (39)	
≥2	167 (25)	137 (26)	30 (23)	
Invasive ventilation, n (%)				<0.001*
Yes	344 (52)	213 (40)	131 (98)	
No	321 (48)	319 (60)	2 (2)	
Limitations on life-sustaining treatments, n (%)				0.001*
Yes	83 (12)	78 (15)	5 (4)	
No	582 (88)	454 (85)	128 (96)	
COVID-19 period, n (%)				ns
Wave 1	265 (40)	218 (41)	47 (35)	
Waves 2–3	400 (60)	314(59)	86 (65)	

Abbreviations: BMI: body mass index; SAPS 3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index score; SD: Standard deviation; ns=no statistically significant differences, *p<0.05 statistically significant differences

Table 2. Risk of death 30 days and 90 days after interhospital transfer among critically ill patients with SARS-CoV-2 presented as hazard ratios with 95% CI (Non-IHT as reference)

Risk of death after interhospital transfers							
	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
All patients	No (%)	30-day No (%)	90-day No (%)	Unadjusted HR with 95% CI	Adjusted HR with 95% CI	Unadjusted HR with 95% CI	Adjusted HR with 95% CI
Non-IHT	532 (80)	136 (26)	157 (30)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	133 (20)	25 (19)	34 (26)	0.66 (0.43–1.02)	0.47 (0.30–0.76)*	0.79 (0.54–1.14)	0.52 (0.34–0.78)*

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (0–1 or >2), mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1/waves 2–3). *Statistically significant differences between groups, p<0.05

Abbreviations: IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

Table 3. The sensitivity analysis presents the risk of 30-day and 90-day mortality following interhospital transfer (IHT), categorised by the length of ICU stay from admission to the day of transfer. The analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI), using non-IHT patients as the reference group.

Risk of death for IHT by the length of ICU stay							
	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
ICU LOS	No (%)	30-day No (%)	90-day No (%)	Unadjusted HR with 95% CI	Adjusted HR with 95% CI	Unadjusted HR with 95% CI	Adjusted HR with 95% CI
>6 days							
Non-IHT	241 (65)	70 (29)	83 (34)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	127 (35)	25 (20)	34 (27)	0.62 (0.39–0.97)*	0.42 (0.26–0.68) *	0.70 (0.47–1.05)	0.45 (0.29–0.69)*
>8 days							
Non-IHT	187 (61)	57(31)	69 (37)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	118 (39)	24(20)	33 (28)	0.61 (0.38–0.98)*	0.40 (0.24–0.67)*	0.69 (0.45–1.04)	0.43 (0.28–0.67)*
>10 days							
Non-IHT	161 (60)	49 (30)	61 (38)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	106 (40)	22 (21)	31 (29)	0.63 (0.38–1.05)	0.46 (0.27–0.78)*	0.71 (0.46–1.09)	0.49 (0.31–0.77)*
>12 days							
Non-IHT	147 (60)	44 (30)	55 (37)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	94 (40)	21 (22)	30 (32)	0.71 (0.42–1.19)	0.48 (0.28–0.85)*	0.80 (0.51–1.25)	0.53 (0.33–0.85)*

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (0, 1, >2), mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1 or waves 2/3). *Statistically significant differences between groups, p<0.05

Abbreviations: LOS: length of stay; ICU: intensive care unit; IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

Table 4. The sensitivity analysis presents the risk of 30-day and 90-day mortality following interhospital transfer (IHT), categorised by pandemic waves. The analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI), using non-IHT patients as the reference group.

Risk of death for IHT by COVID-19 wave							
	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
Waves	No (%)	30-day No (%)	90-day No (%)	Unadjusted HR with 95% CI	Adjusted HR with 95% CI	Unadjusted HR with 95% CI	Adjusted HR with 95% CI
Wave 1							
Non-IHT	218 (82)	61 (28)	64 (29)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	47 (18)	4 (9)	7 (15)	0.26 (0.10–0.73)*	0.24 (0.08–0.66)*	0.44 (0.20–0.96)*	0.38 (0.17–0.85)*
Wave 2-3							
Non-IHT	314 (78)	75 (24)	93 (30)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	86 (22)	21(24)	27 (31)	0.95 (0.58–1.54)	0.68 (0.38–1.18)	1.01 (0.65–1.54)	0.63 (0.38–1.04)

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (1, >2) mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1/wave 2-3). *Statistically significant differences between groups, p<0.05

Abbreviations: IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

Figure 2. Kaplan-Meier curve showing survival to day 30 from ICU admission for patients with SARS-CoV-2 infection in Sweden between 1 March 2020 and 30 June 2021.

Abbreviations: IHT: Interhospital transport

Figure 3. Kaplan-Meier curve showing survival to day 90 from ICU admission for patients with SARS-CoV-2 infection in Sweden between 1 March 2020 and 30 June 2021.

Abbreviations: IHT: Interhospital transport

Figure 4. Days alive and free of ICU within 30 and 90 days among transferred and non-transferred patients.

Abbreviations: IHT: Interhospital transport

File 1. Mortality distribution among transferred patients in relation to the day of transfer.

FIGURES

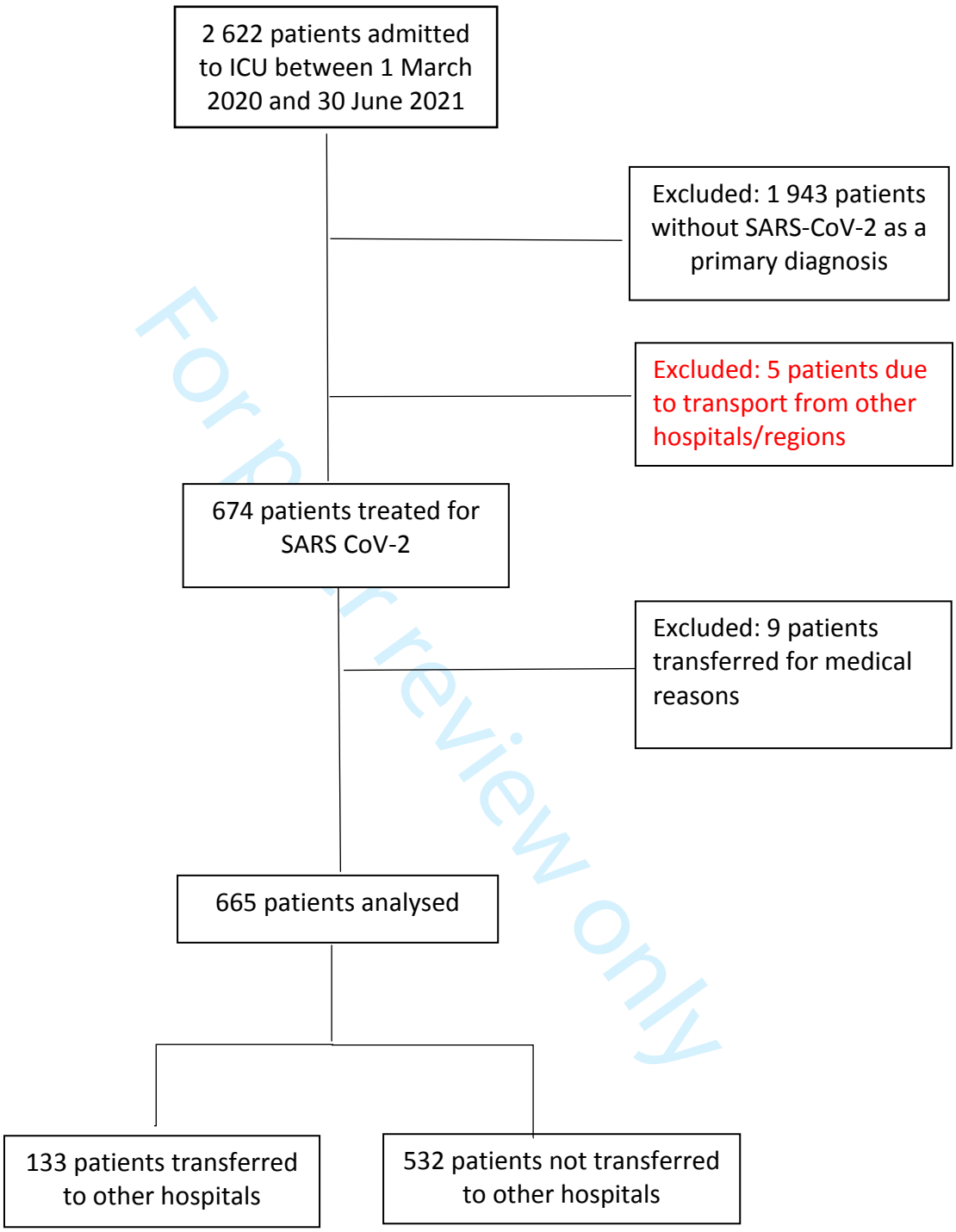
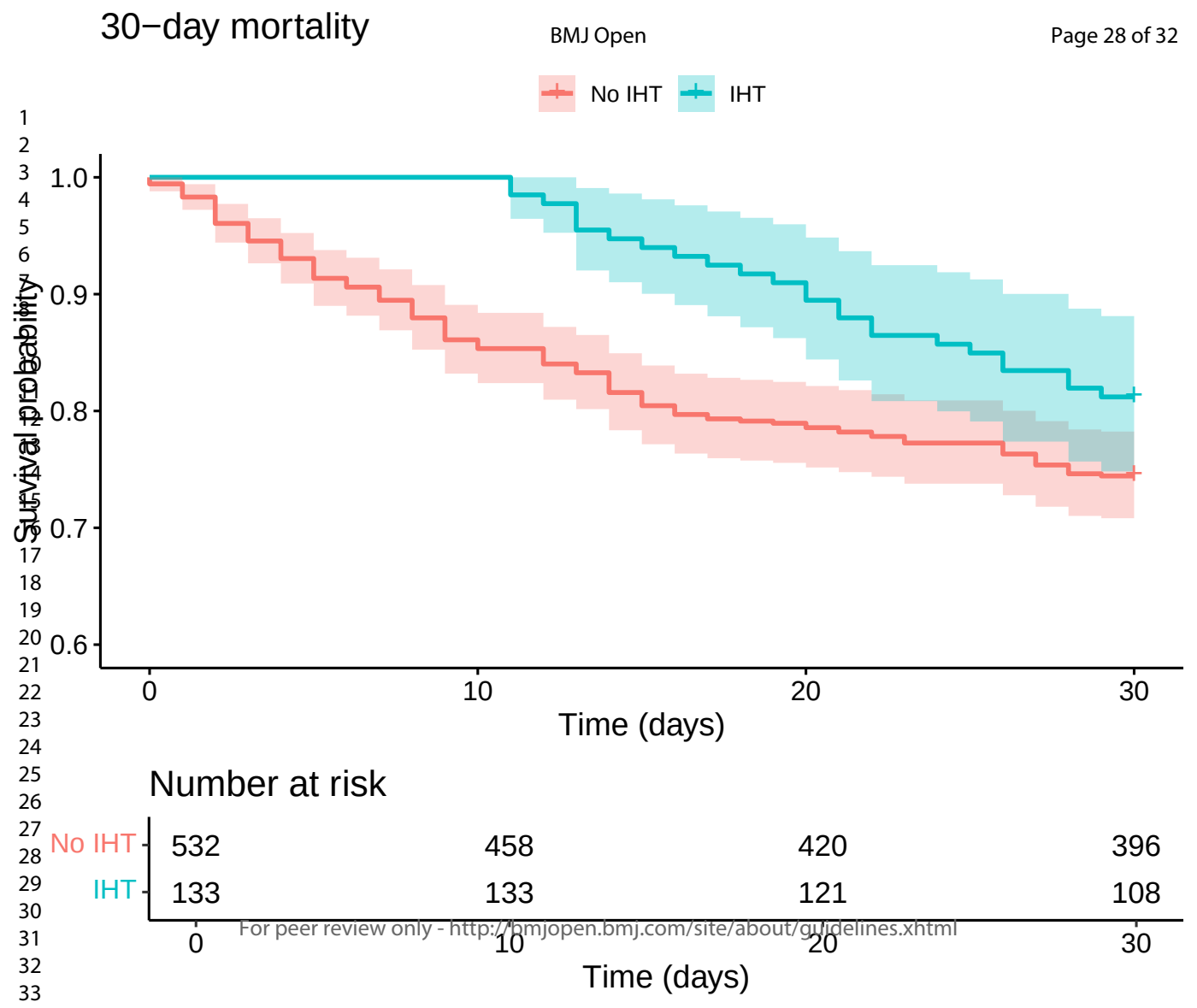
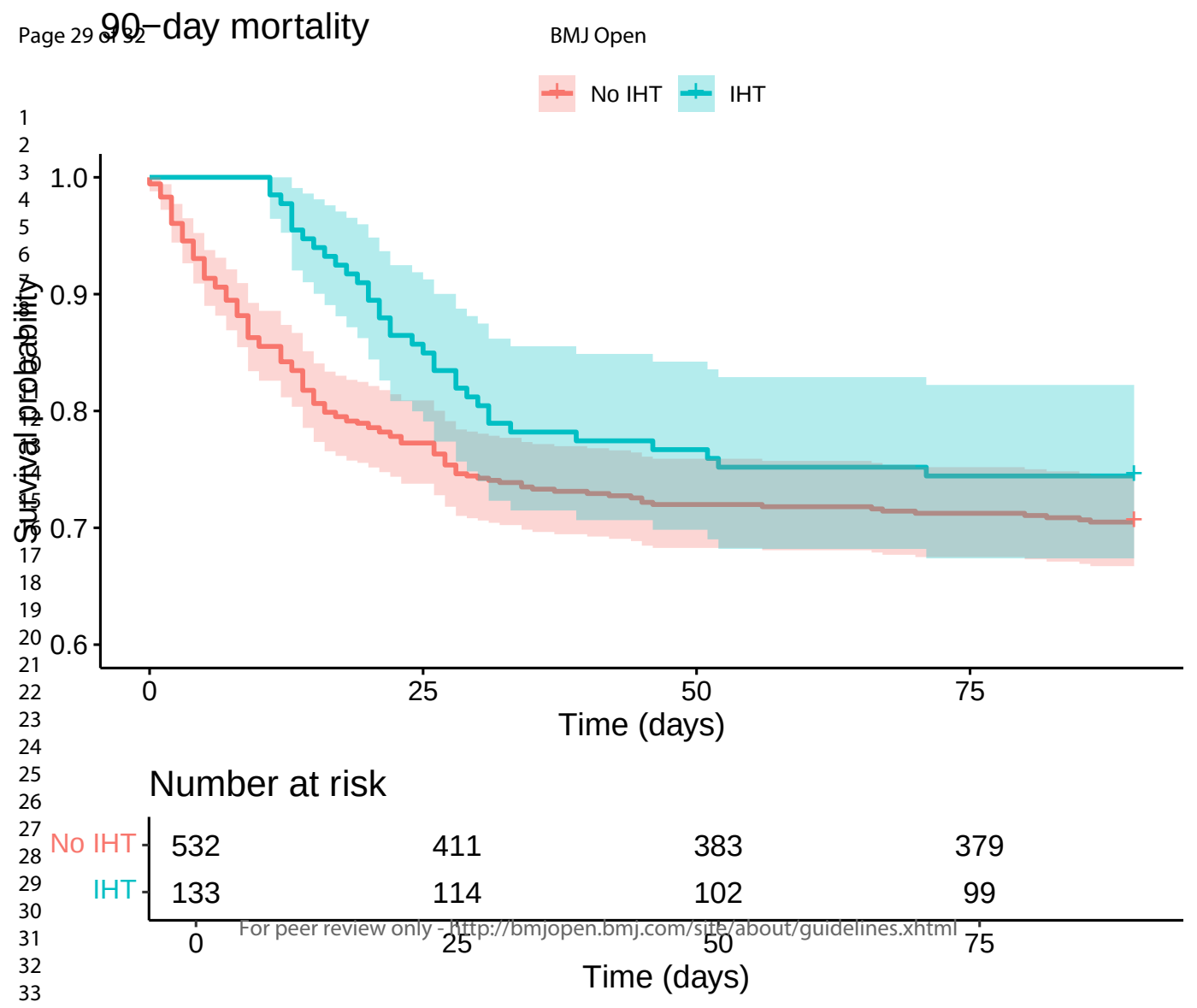
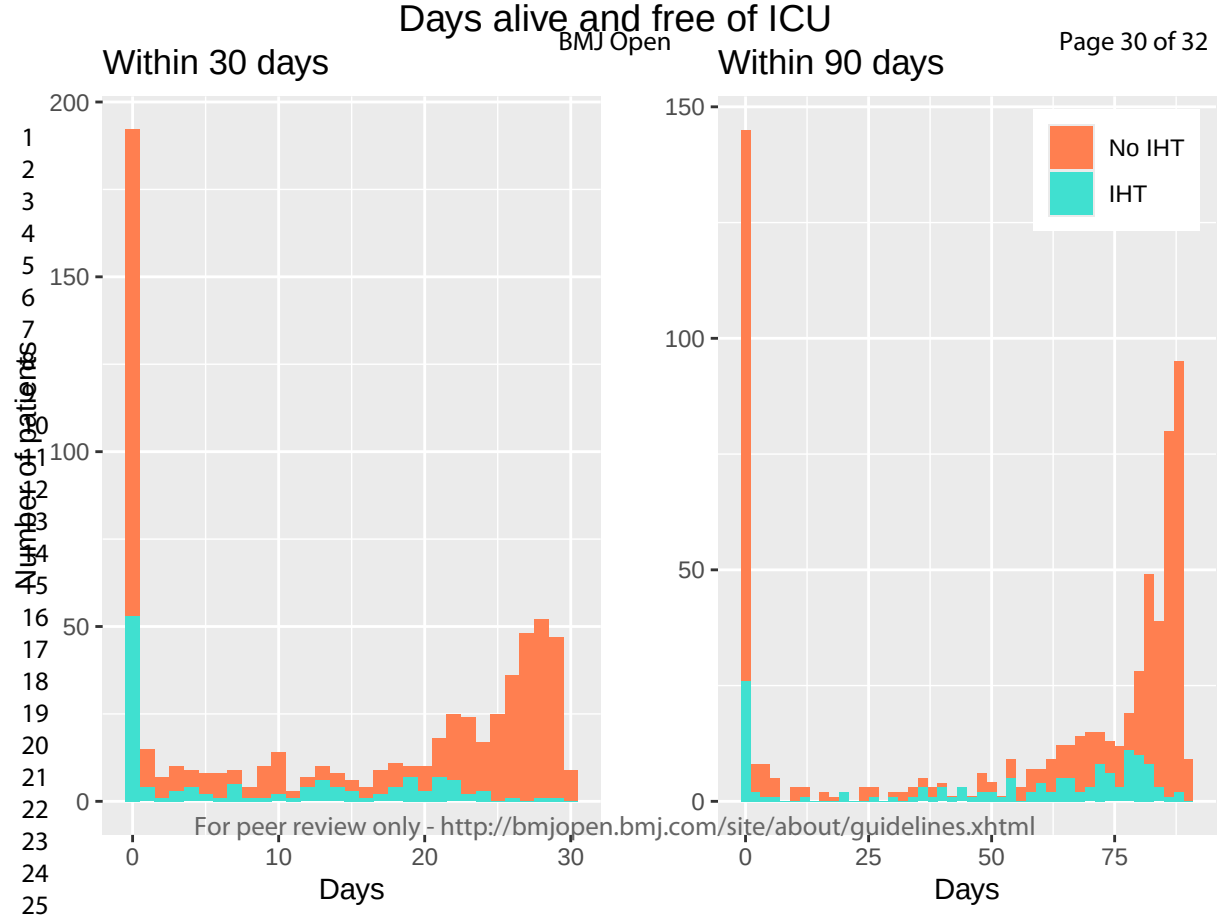


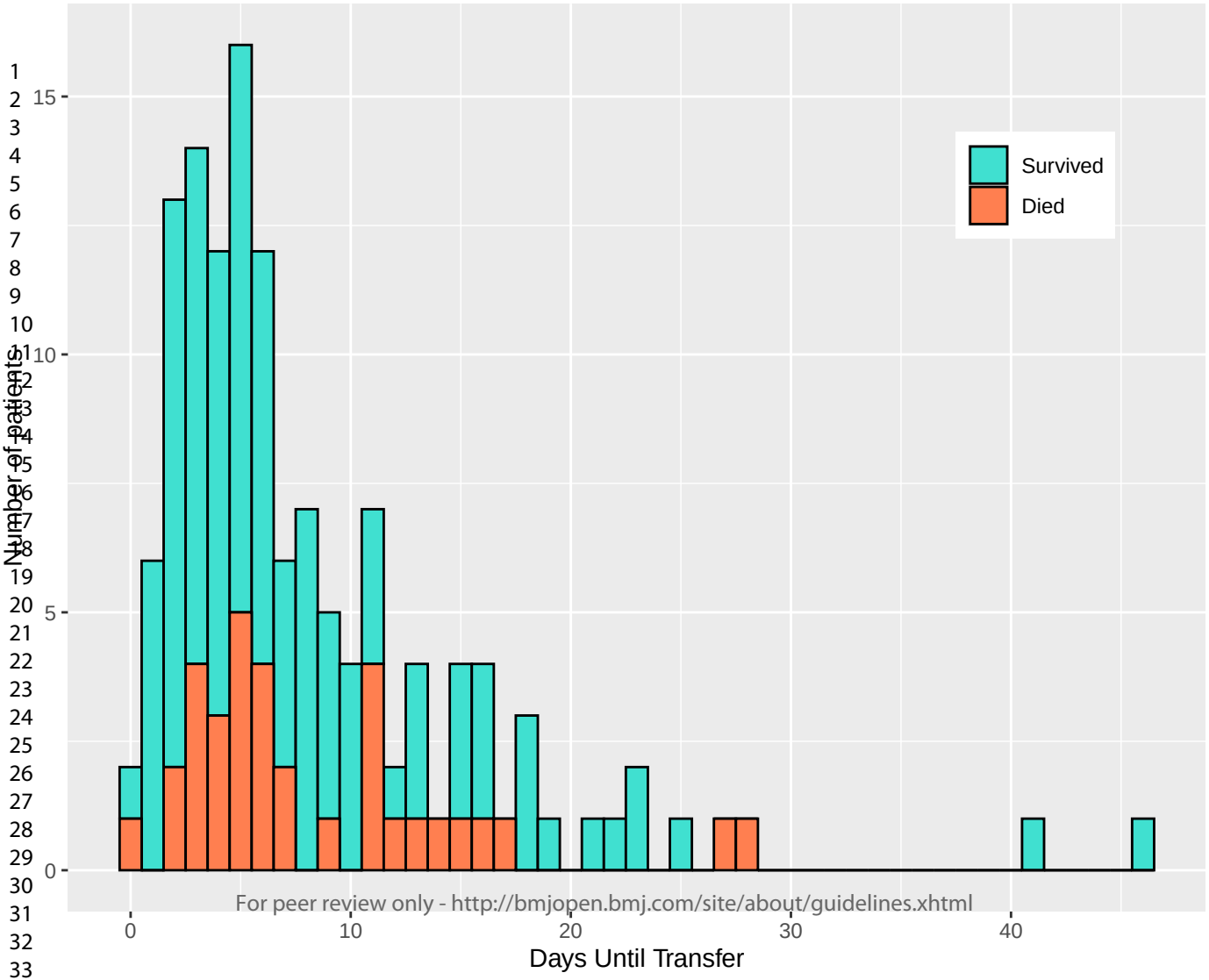
Figure 1. Flowchart of study inclusion







90−day mortality by ICU day of transport



SUPPLEMENTARY FILES

Supplementary File 2

For the group without mechanical ventilation (total 321, 319 without IHT and two with IHT), neither of the two patients with exposure to IHT died within either 30 or 90 days compared to the 66 patients (21%) in the group without mechanical ventilation in the group not exposed to IHT. Due to the small number of patients and no event in the group without mechanical ventilation and IHT, the analyses were neither of interest nor statistically appropriate. When analysing only the subgroup of patients with mechanical ventilation (total 344, 213 without IHT and 131 with IHT), the results showed a reduced risk of death in both the univariate model, HR 0.51 (95% CI 0.32–0.81) for 30-day mortality and HR 0.60 (95% CI 0.40–0.89) for 90-day mortality, and the multivariate model, HR 0.40 (95% CI 0.25–0.65) for 30-day mortality and HR 0.45 (95% CI 0.30–0.68) for 90-day mortality.

For the group with treatment limitations (total 83, 78 without IHT and five with IHT), three patients (60 %) with exposure to IHT died within 30 and 90 days compared to the 55 (66%) and 58 (70%) with no exposure to IHT in 30 and 90 days, respectively. Even though the percentage was about the same in the two groups, the analysis was not carried out due to the small number of patients exposed to IHT with treatment limitations. For the patient group without treatment limitations (total 582, 454 without IHT and 128 with IHT), the results were the same as in the original models, showing no difference between patients without exposure to IHT compared to patients with exposure in the univariate model, HR 0.92 (0.58-1.48) for 30-day mortality and HR 1.08 (95% CI 0.72–1.60) for 90-day mortality, and a difference in the multivariate model, HR 0.38 (95% CI 0.23–0.62) for 30-day mortality and HR 0.45 (95% CI 0.29–0.68) for 90-day mortality.

SUPPLEMENTARY FILES

Supplementary file 3 Characteristics of mechanically ventilated patients admitted to an ICU for SARS-CoV-2 (non-invasive ventilated patients were excluded)

	All patients	Non-IHT patients	IHT patients	p-value
Total number (%)	344	213	131	
Age, median (IQR)	64 (55–71)	64 (55–71)	65 (57–72)	ns
Sex, n (%)				ns
Men	258 (75)	157 (74)	101 (77)	
Women	86 (25)	56 (26)	30 (23)	
BMI, n (%)	(n=341)	(n=210)		ns
>30	139 (41)	89 (42)	50 (38)	
<30	202 (59)	121 (58)	81 (62)	
SAPS 3, median (IQR)	57 (53–63)	57 (53–63)	57 (53–63)	ns
CCI category, n (%)				ns
0	132 (38)	82 (39)	50 (38)	
1	133 (39)	81 (38)	52 (40)	
≥2	70 (23)	50 (23)	29 (22)	
Limitations on life-sustaining treatments, n (%)				ns
Yes	16 (5)	11 (5)	5 (4)	
No	328 (95)	202 (95)	126 (96)	
COVID-19 period, n (%)				0.003*
Wave 1	160 (47)	113 (53)	47 (36)	
Waves 2–3	184 (53)	100 (47)	84 (64)	

Abbreviations: BMI: body mass index; SAPS 3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index score; SD: standard deviation; ns=no statistically significant differences, *p<0.05 statistically significant differences.

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Interhospital transports and mortality in patients with critical COVID-19: a single-centre cohort study

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ABSTRACT

Objectives

This study aimed to compare mortality rates and length of hospital stay between patients with critical COVID-19 transferred to another hospital due to capacity constraints and those who remained at their initial admission hospital.

Design

Single-centre cohort study

Setting and participants

Six hundred and sixty-five patients treated for SARS-CoV-2 at two intensive care units (ICU) in Stockholm, Sweden from 1 March 2020 to 30 June 2021. Data on interhospital transfers were retrieved from medical records and patient data management systems according to pre-defined protocols.

Main outcome measures

The outcomes were 30- and 90-day mortality, days alive and out of ICU. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazard models with adjustments for age, sex, body mass index, severity of illness, comorbidity, invasive ventilation, treatment limitations and pandemic waves.

Results

Of 665 patients, 133 (20%) were transferred to another hospital. The mortality rate for transferred patients compared to non-transferred patients at 30 days was 19% versus 26%

(p=0.13) and at 90 days 26% versus 30% (p = 0.43). In the adjusted Cox regression analysis, interhospital transfer was associated with a lower mortality risk at 30 days (HR 0.47, 95% CI: 0.30–0.76) and 90 days (HR 0.52, 95% CI: 0.34–0.79). However, the number of days alive and out of ICU was significantly lower for the IHT group at 30 days.

Conclusion

In our study, interhospital transfer due to capacity constraints among critically ill COVID-19 patients was not associated with a higher mortality risk. The suitability for transfer was likely associated with lower mortality, although residual confounding cannot be ruled out. The requirement for invasive ventilation among transferred patients might account for the extended length of ICU stay, rather than the transfer itself. However, the difficulty in studying this issue lies in the fact that while patients are likely exposed to risks during transfer, they are simultaneously the patients stable enough to be transported.

Strengths and limitations of this study

- The strengths are the comprehensive data collection conducted by dedicated researchers during the three pandemic waves and validated by independent researchers.
- The low proportion of missing data, and the adjustment for known confounders in the analyses.
- The main weakness is the single-centre non-randomised design.
- There may be a risk of selection bias in the study since it is likely that respiratory – and hemodynamic-stable patients with recovery potential were selected for transport.

- Information about the severity of illness immediately before transport was not readily available in our cohort.

BACKGROUND

Transports of critically ill patients between intensive care units (ICUs) across hospitals are relatively common. The primary reasons include the need to transfer to a hospital with specialised competence, as well as capacity constraints at the transferring hospital [1-3]. Regardless of the reason for the transport, studies have shown that patient transfers entail direct risks related to the transport itself and can be linked to delayed diagnostics or treatments [1 4-8]. In the years before the COVID-19 pandemic, around 600 ICU patients (1.8%) were transported between hospitals in Sweden each year due to resource shortages at the sending ICU. However, during the pandemic, the influx of patients requiring ICU treatment significantly increased interhospital transfers (IHTs) to 3.5% [9].

Studies investigating the risk of IHT during the COVID-19 pandemic have shown conflicting results. Some studies indicate that IHT is not associated with an increased mortality risk [2 10-13] or may even be associated with a lower risk of death [14], whereas others have shown that IHT is associated with a longer duration of mechanical ventilation [10-12], ICU stay [11] and length of hospital stay [2 11 12]. None of these studies were randomised controlled trials, and many were limited by a small sample size [2 10 13]. Despite the large increase in ICU beds in Sweden during the pandemic, a substantial proportion of critically ill patients were transferred between hospitals. To the best of our knowledge, no study has so far studied the influence of IHTs on patient outcomes during the COVID-19 pandemic in Sweden. Therefore, we aimed to compare mortality rates and length of hospital stay between patients transferred to

another hospital due to capacity constraints and those who remained at their initial admission hospital.

METHODS

Study design

This study included all adult patients (age ≥18 years) with confirmed SARS-CoV-2, as verified by polymerase chain reaction test, requiring intensive care at Södersjukhuset, Sweden, between 1 March 2020 and 30 June 2021. The hospital is a secondary referral centre, serving a diverse range of medical and surgical patients in Stockholm, a city with 2.5 million inhabitants. The hospital has a total capacity of 600 beds and houses a large emergency department with a continuous inflow of acutely ill patients. Healthcare in Sweden is predominantly funded by taxes, ensuring access to medical services for all citizens. Normally, there are 18 beds dedicated to intensive care. However, during the COVID-19 pandemic, the ICUs expanded to accommodate a total of 60 ICU beds. The study was approved by the Swedish Ethical Review Authority (Dnr: 2023-01778-01-380347, amendment 2023-01778-01), and the requirement for written informed consent from patients was waived. The reporting of the study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15].

Cohort

All adult patients with a SARS-CoV-2 diagnosis and initial admission at the study hospital's ICU were eligible for inclusion in the study. Patients first admitted to other ICUs and subsequently transferred to the study hospital were excluded. Additionally, patients transferred due to reasons other than capacity constraints, such as repatriation (return to a local ICU near the patient's home) and clinical transfers (requiring specialized care not available at the admitting hospital) were excluded from the study.

Patients were identified using the patient data management system. Clinical data were automatically and manually extracted from medical records and the patient data management system using a pre-defined data collection protocol to ensure consistency and uniformity of the data collection. Cross-validation of data from randomly selected patients was performed separately by two independent researchers.

Exposure

The exposure was Interhospital Transfer (IHT), specifically defined as the transfer of patients from the Intensive Care Unit (ICU) at the index hospital to another hospital's ICU due to capacity constraints. These constraints typically involve a shortage of staffed ICU beds at the referring hospital, necessitating the transfer of patients to ensure they receive the critical care they need.

The interhospital transfers were conducted in accordance with the transport recommendations provided by the Swedish Society for Anaesthesia and Intensive Care. These guidelines ensure that transfers are carried out safely and efficiently, minimising risks to the patient during transport. The guidelines cover various aspects, such as patient stability before the transfer, necessary medical equipment during the transfer, and the qualifications of the medical personnel accompanying the patient. The transfers were crucial for managing ICU capacity and ensuring that patients continue to receive appropriate care without delay [16]. The selection of patients for transfer was commonly carried out in consultation with the admitting ICU. The decision was based on the patient's physiological status to ensure safe transport and the receiving hospital's capacity to provide the required care. This process did not adhere to a standardized protocol or guideline; rather, it relied on the clinical judgment of senior physicians, who made joint decisions about which patient was most suitable for

transfer, based on various clinical factors and the urgency of the situation. The decision-making process involved assessing the patient's condition, stability, and the potential risks and benefits of transfer aiming to ensure that the patient most in need of ICU care at another facility was selected for transfer, taking into consideration the overall capacity and resources of both the referring and receiving hospitals. The lack of a standardized protocol meant that decisions were tailored to individual cases relying of clinical expertise and teamwork in managing ICU capacity and patient care.

The transport was prepared according to local routines, and handover was reported by telephone. ICU patients in Stockholm are commonly transported between hospitals using a mobile intensive care unit (MICU). A MICU is staffed with one ambulance nurse, one paramedic and one physician from the departing intensive care unit. The MICU transporter is more spacious than a standard ambulance and is equipped with continuous electrocardiography monitoring, invasive hemodynamic monitoring and advanced ventilatory support. Information about the date, time and reasons for transfer was obtained from the patient's medical records and the patient data management system.

Outcomes

The outcomes were mortality at days 30 and 90 from ICU admission and days alive and out of ICU. The length of ICU stay was measured from the date of ICU admission to the date of discharge from the ICU at Södersjukhuset or the admitting hospital.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables are expressed as numbers and proportions (percentages). The distribution of continuous variables was tested with the Shapiro-Wilk test. Differences between groups were analysed using the Mann-Whitney U test and the Chi^2 test for continuous and categorical variables, respectively.

In the survival analyses, patients were followed up from the date of ICU admission until the date of death or until 30 and 90 days had passed since admission. Kaplan–Meier curves were used to estimate the cumulative risk of death, and the log-rank test was employed to compare patients with exposure to IHT versus those without IHT. Cox proportional hazards regression was used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) for death within 30 and 90 days from ICU admission. Multivariate models were adjusted for age (continuous), sex (male/female), body mass index (<30/≥30 kg/m^2), Simplified Acute Physiology Score III (SAPS III) (>50/50–59/≥60), Charlson Comorbidity Index (categorised as 0/1/2) [17], invasive mechanical ventilation (yes/no), treatment limitations (yes/no), COVID waves (first wave, March to September 2020 versus second and third waves, October 2020 to January 2021 and February to June 2021 [18]) and IHT (yes/no). Both crude and multivariable models were investigated with no IHT as the reference group. Scaled Schoenfeld residuals were regressed against survival time to assess the proportional hazard assumptions, and Martingale residual plots, together with the Grambsch-Therneau test, were used to assess evidence of non-linearity. Variance inflation factors were used when investigating multicollinearity. All variables were complete except for SAPS and BMI which were missing for 105 and 6 patients, respectively. This was handled by a separate category for patients with missing values.

Since the proportional hazards assumption in the Cox regression was not met, indicating that the effect of the variables could vary over time, we performed sensitivity analyses on subgroups of patients based on length of ICU stay (more than 6, 8, 10 and 12 days), COVID waves, mechanical ventilation, and treatment limitations. Comparisons of days alive free from ICU were conducted using the Mann-Whitney U test and presented as medians with interquartile ranges (IQRs).

A two-sided p-value less than 0.05 was considered statistically significant. The analysis followed a predefined protocol and was conducted using the IBM SPSS Statistics version 29 statistical software and R version 4.3.3 (R Core, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). All analyses were discussed and confirmed with an experienced biostatistician.

RESULTS

Patient cohort

Of 2622 critically ill patients admitted to the two ICUs during the study period, 674 had a confirmed SARS-CoV-2 diagnosis. Nine patients were transported to other hospitals for tertiary care (e.g. ECMO) and five patients had been transferred to the study hospital from other hospitals/regions. In total, 665 SARS-CoV-2 patients were included in the study, of which 133 (20%) underwent interhospital transports due to capacity constraints (Figure 1). All patients (n=133) were transported to a hospital within a 30-kilometer radius or maximum of 30 minutes.

The median age of included patients was 64 years, and most were men (72%). Patients who were transferred were more often on mechanical ventilation (98%) compared with the non-transferred patients (40%), and fewer had limitations in terms of life-sustaining treatment (4% versus 15%). Otherwise, the groups were balanced regarding patient and clinical characteristics (Table 1). The median day of IHT from admission was 6 (IQR: 3–11).

Interhospital capacity transfer and mortality

Analyses and distribution of IHT and mortality in patients with critical COVID-19 are shown in Table 2 and Supplementary file 1. Mortality rates did not differ between groups at either 30 days (19% vs. 26%, p = 0.13) or 90 days (26% vs. 30%, p = 0.43). This was consistent across the log-rank test for survival for 30 days (Figure 2, p = 0.06) and 90 days (Figure 3, p = 0.2), as well as the HR of the univariate Cox regression of 0.66 (95% CI: 0.43–1.02) for 30-day mortality and 0.79 (95% CI: 0.54–1.14) for 90-day mortality. When the exposure of IHT was

analysed in the multivariate model, it was associated with a lower risk of mortality for both 30 days (HR 0.47, 95% CI: 0.30–0.76) and 90 days (HR 0.52, 95% CI: 0.34–0.79) (Table 2).

As the assumptions of proportional hazards were violated when scaled Schoenfeld residuals were regressed against survival time ($p < 0.001$ for the multivariate model for 30- and 90-day mortality), sensitivity analyses were performed. When splitting the time and analysing by different lengths of stay (LOS) at the ICU, the assumptions were fulfilled for patients with an LOS of eight days and above ($p = 0.14$ for 30-day mortality and $p = 0.09$ for 90-day mortality). The results did not differ from the original models except for IHT being associated with lower 30-day mortality, including in the univariate analyses for patients with an ICU LOS of more than six and eight days (Table 3). Schoenfeld residuals indicated violations of proportional hazard assumptions, including for the covariates of mechanical ventilation, treatment limitations and COVID-19 wave in the multivariate models for 30 and 90 days. This issue was addressed by examining the various categories within these variables as subgroups. The reason for the violation of the variables of mechanical ventilation and treatment limitations was a small number of patients/events in the groups of patients without mechanical ventilation exposed to IHT and the group with treatment limitations exposed to IHT (See details in Supplementary file 2 and 3). When analysing the subgroup of only mechanically ventilated patients, the results changed in the univariate models, showing a lower risk of mortality for 30 days (19.3% versus 32.9%, p=0.008) and 90 days (26.0% versus 38.0%, p=0.029) in the IHT group compared to the non-IHT group. In the multivariate models, the decrease in mortality for the IHT group at 30 and 90 days remained unchanged. Excluding patients with treatment limitations did not change the results.

Interhospital capacity transfer and mortality by COVID-19 wave

For the group of patients treated during the first COVID-19 wave, the univariate analyses for 30-day mortality indicated a reduction in deaths for the IHT group, with a hazard ratio (HR) of 0.26 (95% CI: 0.10–0.73). The univariate analyses for 90-day mortality and the multivariate analyses for both 30- and 90-day mortality remained consistent, with HRs of 0.44 (95% CI: 0.20–0.96), 0.24 (95% CI: 0.08–0.66), and 0.38 (95% CI: 0.17–0.85), respectively (Table 4).

For the group treated during the second and third COVID-19 waves, the results differed from the original multivariate models. In this subgroup, there was still no significant difference between patients with and without IHT in the univariate models, with HRs of 0.95 (95% CI: 0.58–1.54) for 30-day mortality and 1.01 (95% CI: 0.65–1.54) for 90-day mortality. However, unlike the findings in the whole cohort, there was no longer a significant difference in the associated risk of 30- and 90-day mortality in the multivariate models, with HRs of 0.68 (95% CI: 0.38–1.18) and 0.63 (95% CI: 0.38–1.04), respectively (Table 4).

Interhospital transfer and days alive free of ICU

In unadjusted analyses, IHT patients had a median of fewer days alive and free from the ICU at 30 days compared to non-IHT patients (5, IQR: 0–18 versus 22, IQR: 0–27, p<0.001). At 90 days, there were no statistically significant differences (Figure 4). In the subgroup of mechanically ventilated patients, no significant median differences were observed at either 30 or 90 days.

DISCUSSION

In this study, transfers solely due to capacity constraints during the COVID-19 pandemic were not associated with a higher risk of 30- and 90-day mortality among patients with critical COVID-19. Our results indicated that such transfers may even be associated with a lower mortality risk, especially for mechanically ventilated patients. Interhospital transfer was associated with a longer ICU LOS compared with patients who remained in the admitting ICU. This was probably explained by the higher prevalence of invasive ventilation among transferred patients.

The risk of interhospital transfer has been investigated to some extent in observational studies, albeit with conflicting results. A Swedish register-based study of 2,912 capacity-transferred ICU patients before the pandemic found that transportation was associated with a lower risk of death within 90 days (odds ratio 0.71, 95% CI: 0.65–0.79) [19]. Conversely, another Swedish study including 11,176 ICU patients showed a higher risk of 30-day mortality after capacity transfers (odds ratio 1.25, 95% CI: 1.06–1.49) and clinical transfers (odds ratio 1.17, 95% CI: 1.02–1.36) [20]. However, the reference consisted of repatriated patients. While we excluded such patients in our study, other studies have confirmed that clinical transfer to a higher level of care is associated with better patient outcomes [21 22]. A French cohort study of 18,348 COVID-19 patients in the ICU found that transferred patients had a lower mortality rate than non-transferred patients, concluding that this might be due to a rigorous selection process of patients eligible for transfer [14]. However, the study only included patients from the first wave of the pandemic. This finding resembles ours, where the results were driven by lower mortality in IHT patients during the first COVID wave. A retrospective cohort study including 5,207 patients mostly with SARS-CoV-2 during wave 3 of the pandemic in Australia found no association between IHT and mortality [11]. The difference

in outcomes between the pandemic waves may be attributed to changes in healthcare conditions among patients and the accumulated experience in managing the disease. Although capacity constraints remained high during the pandemic waves, the outcomes improved due to the learning curve in treating COVID-19 patients and the implementation of standardized treatments.

Combining the findings of the present study with the previous literature makes it reasonable to argue that IHT of ICU patients does not appear to increase mortality. Nevertheless, there may be other drawbacks to IHTs, such as hospital-acquired infections, discontinued care, information gaps or patients being intubated to ensure safe transport, which may prolong the hospital stay [23 24].

The observed absence of increased mortality risk associated with the transfer may be explained by the fact that patients with recovery potential were carefully selected to be stable enough to tolerate transport safely. This aligns with the results from the above-mentioned French study [14]. Furthermore, the technical difficulties associated with transporting patients with high-flow oxygen therapy with high oxygen fractions most likely contributed to the decision to avoid such transfers, which was reflected in our study where mechanical ventilation was more common in the transferred group.

The main methodological strengths of this study were the comprehensive data collection conducted by dedicated researchers during the three pandemic waves and validated by independent researchers, the low proportion of missing data, and the adjustment for known confounders in the analyses. Among the main weaknesses are the single-centre design and

the non-randomised design. There may be a selection bias in the study, with patients on invasive ventilation and therefore with a secured airway and having limitations of care to a lesser extent, such as do not resuscitate orders, in the transferred group. This difference might explain the lower OR for mortality in the adjusted analysis and also the longer ICU LOS, as the treatments were not discontinued. In this study, we selected mortality and days alive and out of the ICU as one of the outcome measures. However, we acknowledge that organ support-free days could have been another valuable parameter to assess the impact of transfers. This alternative measure could provide additional insights into the safety of interhospital transfers. Assessing illness during transport and comparing different patient groups presents several challenges. Information about the severity of illness immediately before transport, which might be more appropriate to include in the analyses than the severity of illness at ICU admission, was not readily available. We did not find sufficient and reliable data to analyse this in our cohort. Furthermore, we used SAPS III to assess illness severity instead of the more commonly used systems like APACHE II or IV. SAPS III is the standard scoring system for intensive care patients in Sweden and is utilised for reporting to the Swedish Intensive Care Register (SIR), ensuring consistency and accuracy within the national context. However, this choice may limit the direct comparability of our results with studies using other scoring systems. Fourteen per cent of SAPS data were missing. The missingness was primarily due to manual documentation processes during the pandemic, leading to a gap at one of the ICUs. This gap was likely caused by work-related issues rather than patient-related factors. Patients across the two ICUs were similar in clinical characteristics and diagnoses, and all other variables were complete, supporting the assumption that the missing data were random. We also conducted a sensitivity analysis

with complete cases and the results remained unchanged. Another issue was that lifestyle factors such as smoking, physical activity, and alcohol consumption, as well as socio-economic variables like deprivation, education, and employment status, were not available in our dataset. As such, we were unable to adjust for these variables in the analysis. Furthermore, we have not investigated patients' functional status after ICU discharge, which is of high importance for evaluating surviving patients' well-being.

Differences in mortality between countries may depend on variations in healthcare structure and the degree of burden that the country and the healthcare organisation experienced during the pandemic. Well-established routines for transport, availability of advanced medical transport equipment, and access to the same electronic patient data management systems for transferring and admitting centres may also influence the safety of transport. The findings of this study may be somewhat representative to countries with comparable population structures, healthcare systems, and pandemic responses. The use of standardised healthcare protocols ensures consistency in patient care and treatment, which can make the results of this study applicable to other regions facing similar challenges. Future studies should focus on whether certain patient characteristics are predictive of safe transfers and should study the effects of transfers on surviving patients' ability to recover. Furthermore, it is important to explore various types of complications related to IHT and long-term outcomes to identify factors that may influence treatment outcomes and thereby improve care.

CONCLUSIONS

In our study interhospital transfer due to capacity constraints among critically ill COVID-19 patients was not associated with a higher mortality risk. The suitability for transfer was likely

associated with lower mortality, although residual confounding cannot be ruled out. The requirement for invasive ventilation among transferred patients might account for the extended length of ICU stay, rather than the transfer itself. However, the difficulty in studying this issue lies in the fact that while patients are likely exposed to risks during transfer, they are simultaneously the patients stable enough to be transported.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

KB: Conceptualisation, methodology, design, analysis, writing the original draft, review and editing. LTA: Conceptualisation, methodology, design, writing the original draft, review and editing. PS: conceptualisation, methodology, design, review and editing. MC: Conceptualisation, methodology, design, review and editing. SJ: conceptualisation, methodology, design, analysis, review and editing. EJA: conceptualisation, methodology,

design, review and editing. AS: conceptualisation, methodology, design, analysis, writing the original draft, review and editing. AS: are responsible for the overall content as guarantor.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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Table 1. Characteristics of patients admitted to an ICU for SARS-CoV-2

	All patients	Non-IHT patients	IHT patients	p-value
Total number (%)	665	532 (80)	133 (20)	
Age, median (IQR)	64 (55–72)	64 (55–72)	65 (57–71)	ns
Sex, n (%)				ns
Men	479 (72)	376 (71)	103 (77.4)	
Women	186 (28)	156 (29)	30 (23)	
BMI, n (%)				ns
>30	253(38)	202 (38)	51 (38)	
<30	406 (62)	324 (61)	82 (62)	
SAPS 3, mean ± SD		58 (47–67)	57 (49–65)	ns
CCI category, n (%)				ns
0	248 (37)	197 (37)	51 (38)	
1	250 (38)	198 (37)	52 (39)	
≥2	167 (25)	137 (26)	30 (23)	
Invasive ventilation, n (%)				<0.001*
Yes	344 (52)	213 (40)	131 (98)	
No	321 (48)	319 (60)	2 (2)	
Limitations on life-sustaining treatments, n (%)				0.001*
Yes	83 (12)	78 (15)	5 (4)	
No	582 (88)	454 (85)	128 (96)	
COVID-19 period, n (%)				ns
Wave 1	265 (40)	218 (41)	47 (35)	
Waves 2–3	400 (60)	314(59)	86 (65)	

Abbreviations: BMI: body mass index; SAPS 3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index score; SD: Standard deviation; ns=no statistically significant differences, *p<0.05 statistically significant differences

Table 2. Risk of death 30 days and 90 days after interhospital transfer among critically ill patients with SARS-CoV-2 presented as hazard ratios with 95% CI (Non-IHT as reference)

Risk of death after interhospital transfers							
	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
All patients	No (%)	30-day No (%)	90-day No (%)	Unadjusted HR with 95% CI	Adjusted HR with 95% CI	Unadjusted HR with 95% CI	Adjusted HR with 95% CI
Non-IHT	532 (80)	136 (26)	157 (30)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	133 (20)	25 (19)	34 (26)	0.66 (0.43–1.02)	0.47 (0.30–0.76)*	0.79 (0.54–1.14)	0.52 (0.34–0.78)*

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (0–1 or >2), mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1/waves 2–3). *Statistically significant differences between groups, p<0.05

Abbreviations: IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

Table 3. The sensitivity analysis presents the risk of 30-day and 90-day mortality following interhospital transfer (IHT), categorised by the length of ICU stay from admission to the day of transfer. The analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI), using non-IHT patients as the reference group.

Risk of death for IHT by the length of ICU stay							
	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
ICU LOS	No (%)	30-day No (%)	90-day No (%)	Unadjusted HR with 95% CI	Adjusted HR with 95% CI	Unadjusted HR with 95% CI	Adjusted HR with 95% CI
>6 days							
Non-IHT	241 (65)	70 (29)	83 (34)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	127 (35)	25 (20)	34 (27)	0.62 (0.39–0.97)*	0.42 (0.26–0.68) *	0.70 (0.47–1.05)	0.45 (0.29–0.69)*
>8 days							
Non-IHT	187 (61)	57(31)	69 (37)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	118 (39)	24(20)	33 (28)	0.61 (0.38–0.98)*	0.40 (0.24–0.67)*	0.69 (0.45–1.04)	0.43 (0.28–0.67)*
>10 days							
Non-IHT	161 (60)	49 (30)	61 (38)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	106 (40)	22 (21)	31 (29)	0.63 (0.38–1.05)	0.46 (0.27–0.78)*	0.71 (0.46–1.09)	0.49 (0.31–0.77)*
>12 days							
Non-IHT	147 (60)	44 (30)	55 (37)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	94 (40)	21 (22)	30 (32)	0.71 (0.42–1.19)	0.48 (0.28–0.85)*	0.80 (0.51–1.25)	0.53 (0.33–0.85)*

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (0, 1, >2), mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1 or waves 2/3). *Statistically significant differences between groups, p<0.05

Abbreviations: LOS: length of stay; ICU: intensive care unit; IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

Table 4. The sensitivity analysis presents the risk of 30-day and 90-day mortality following interhospital transfer (IHT), categorised by pandemic waves. The analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI), using non-IHT patients as the reference group.

Risk of death for IHT by COVID-19 wave							
	Exposure	Mortality		**30-day mortality**		**90-day mortality**	
Waves	No (%)	30-day No (%)	90-day No (%)	Unadjusted HR with 95% CI	Adjusted HR with 95% CI	Unadjusted HR with 95% CI	Adjusted HR with 95% CI
Wave 1							
Non-IHT	218 (82)	61 (28)	64 (29)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	47 (18)	4 (9)	7 (15)	0.26 (0.10–0.73)*	0.24 (0.08–0.66)*	0.44 (0.20–0.96)*	0.38 (0.17–0.85)*
Wave 2-3							
Non-IHT	314 (78)	75 (24)	93 (30)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IHT	86 (22)	21(24)	27 (31)	0.95 (0.58–1.54)	0.68 (0.38–1.18)	1.01 (0.65–1.54)	0.63 (0.38–1.04)

The models were adjusted for age, sex, BMI categories (<30 or >30), SAPS, Charlson Comorbidity Index (1, >2) mechanical ventilation (yes/no), treatment limitations (yes/no) and SARS-CoV-2 wave (wave 1/wave 2-3). *Statistically significant differences between groups, p<0.05

Abbreviations: IHT: inter-hospital transfer; HR: hazard ratio; CI: confidence interval

- Figure 1. Flowchart of study inclusion
- Figure 2. Kaplan-Meier curve showing survival to day 30 from ICU admission for patients with SARS-CoV-2 infection in Sweden between 1 March 2020 and 30 June 2021.Abbreviations: IHT: Interhospital transport
- Figure 3. Kaplan-Meier curve showing survival to day 90 from ICU admission for patients with SARS-CoV-2 infection in Sweden between 1 March 2020 and 30 June 2021. Abbreviations: IHT: Interhospital transport
- Figure 4. Days alive and free of ICU within 30 and 90 days among transferred and non-transferred patients. Abbreviations: IHT: Interhospital transport
- Supplementary File 1. Figure displaying 90-day mortality by ICU day of transfer
- Supplementary File 2. Subgroup analysis regarding mechanical ventilation and treatment limitations.
- Supplementary File 3. Characteristics of mechanically ventilated patients

FIGURES

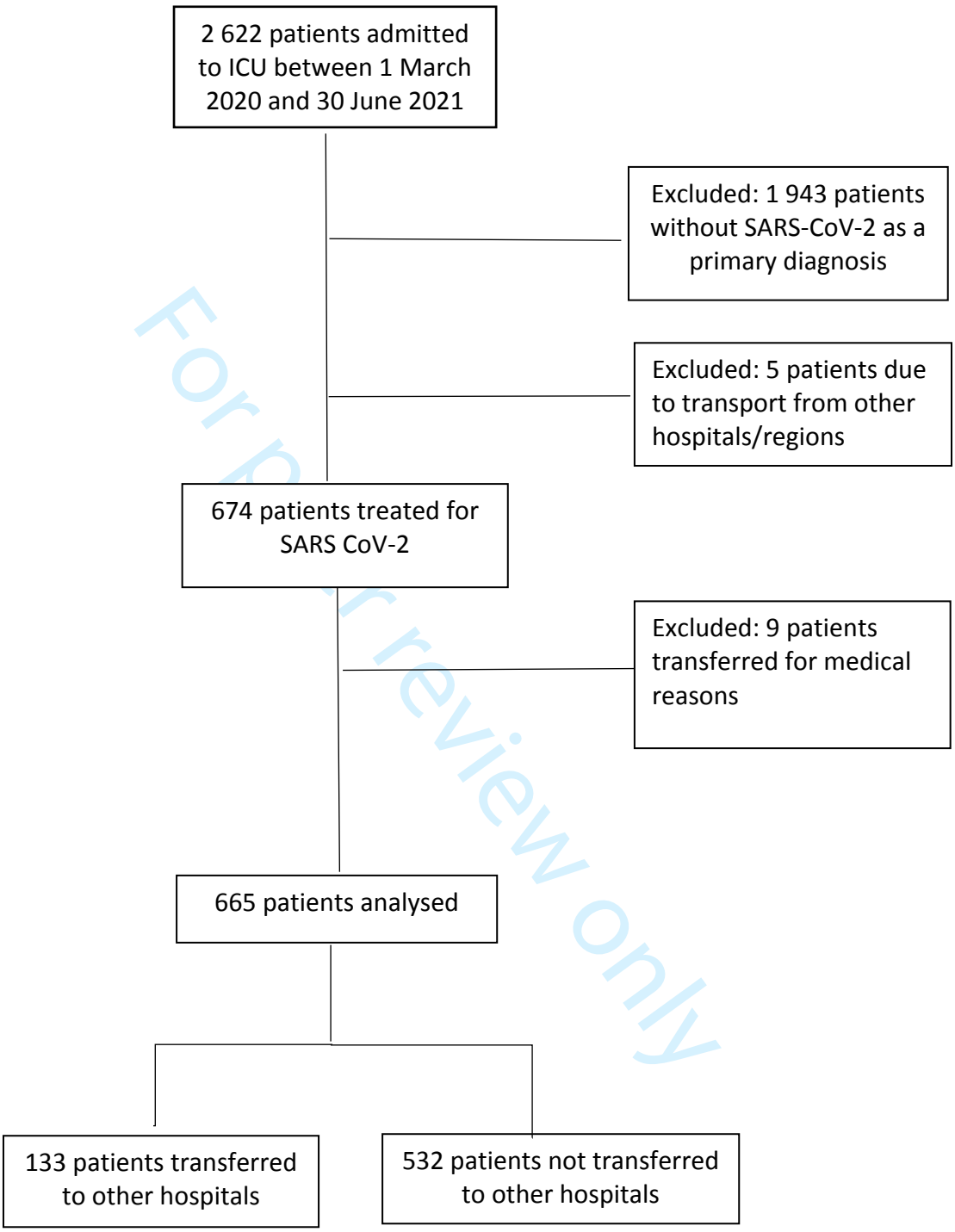
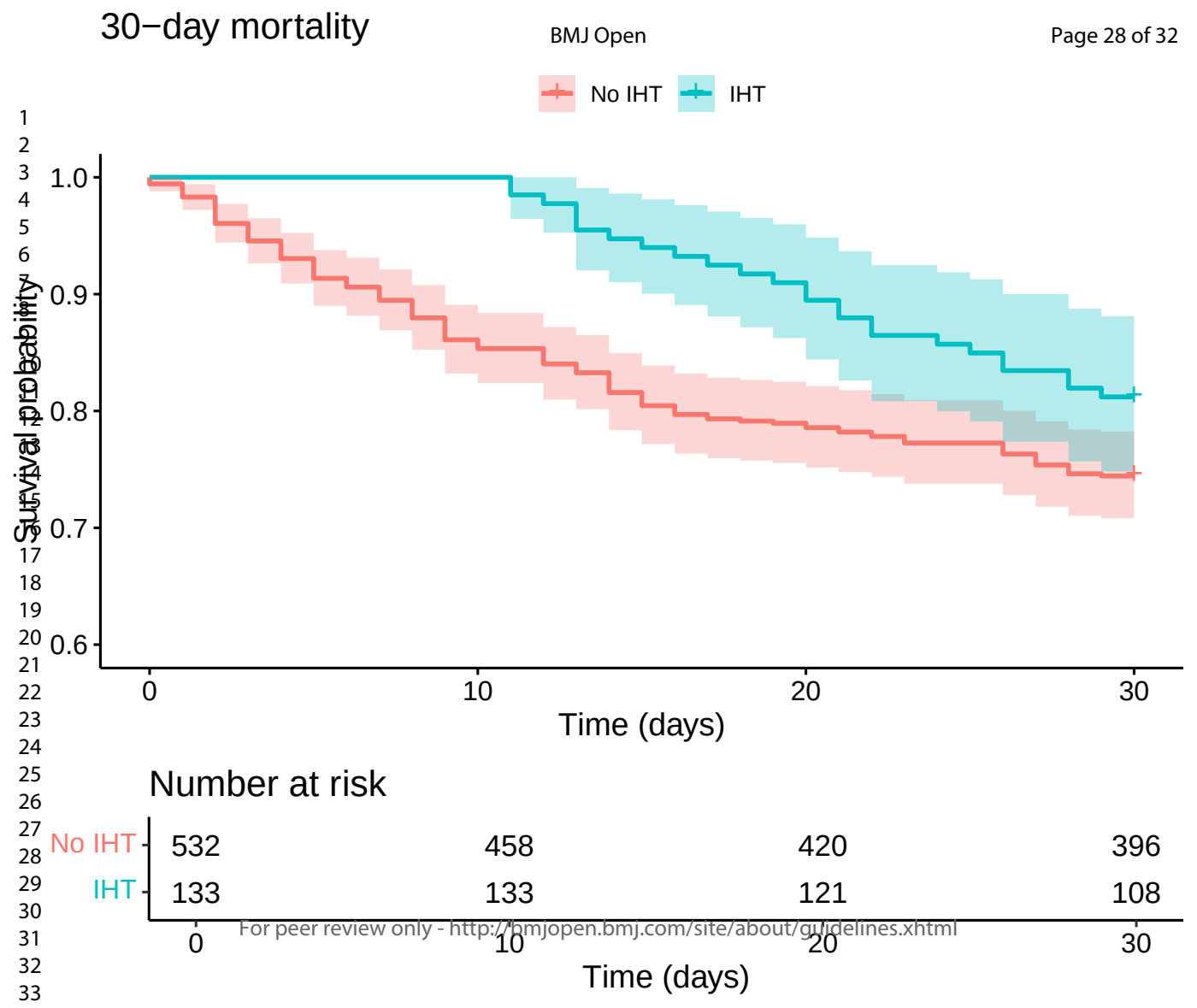
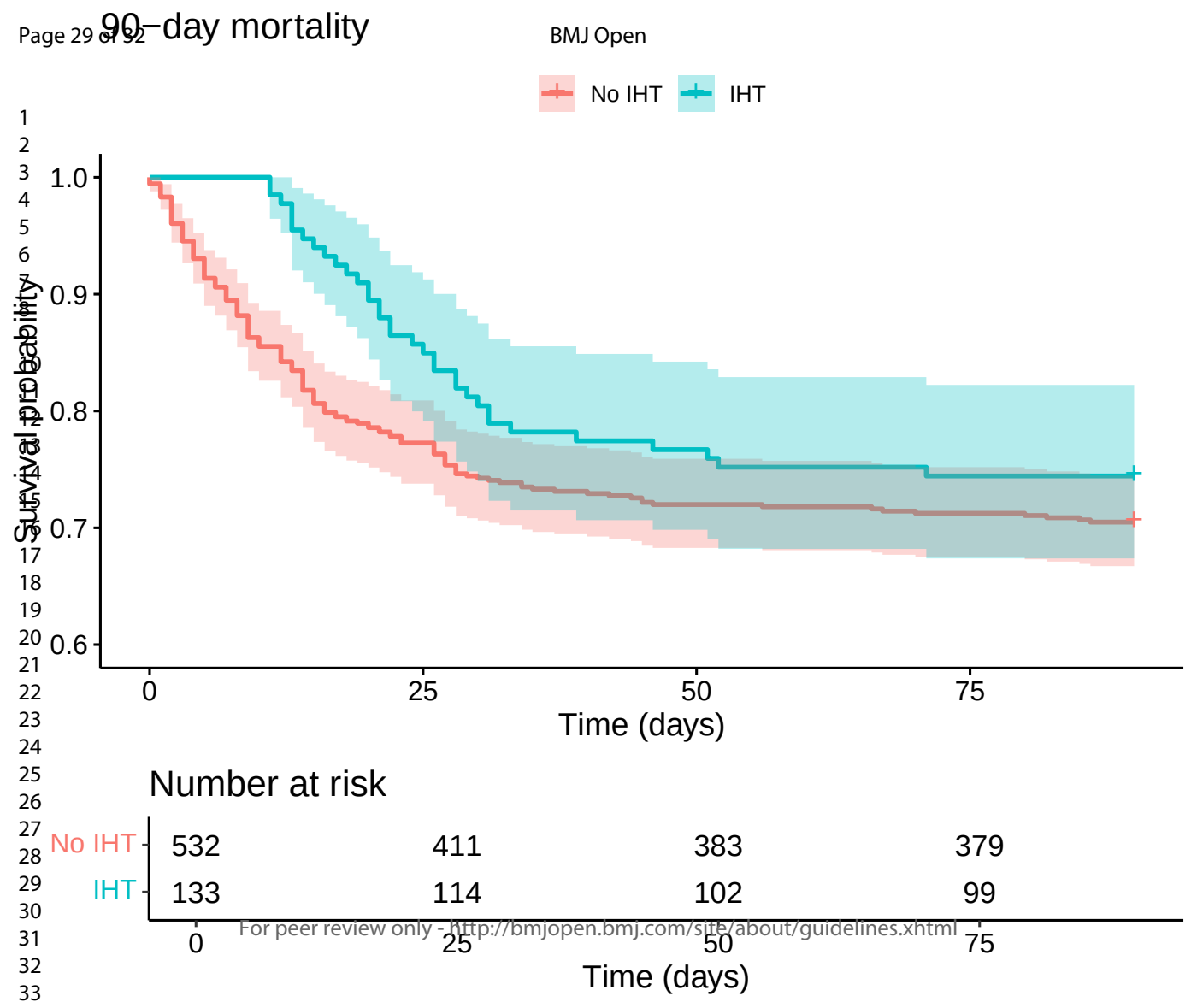
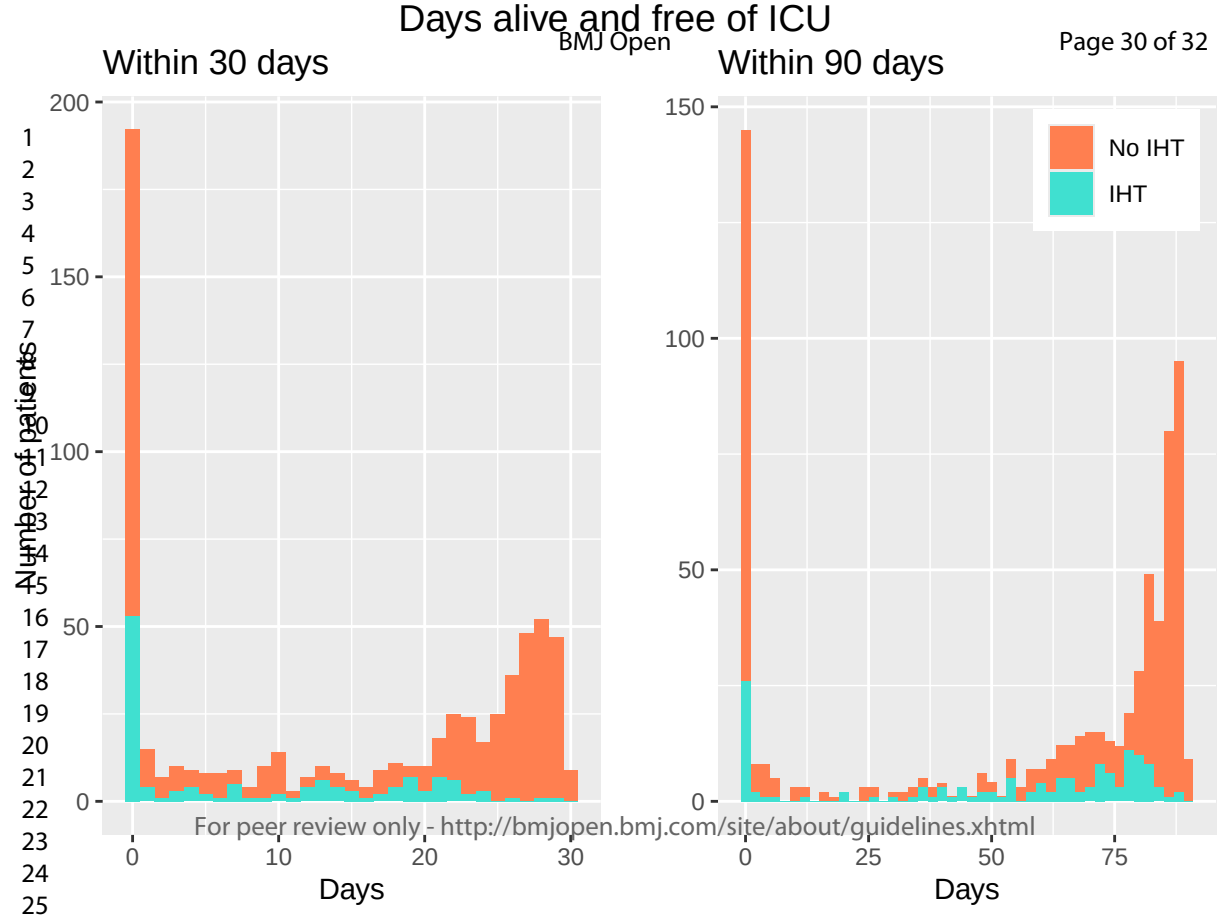


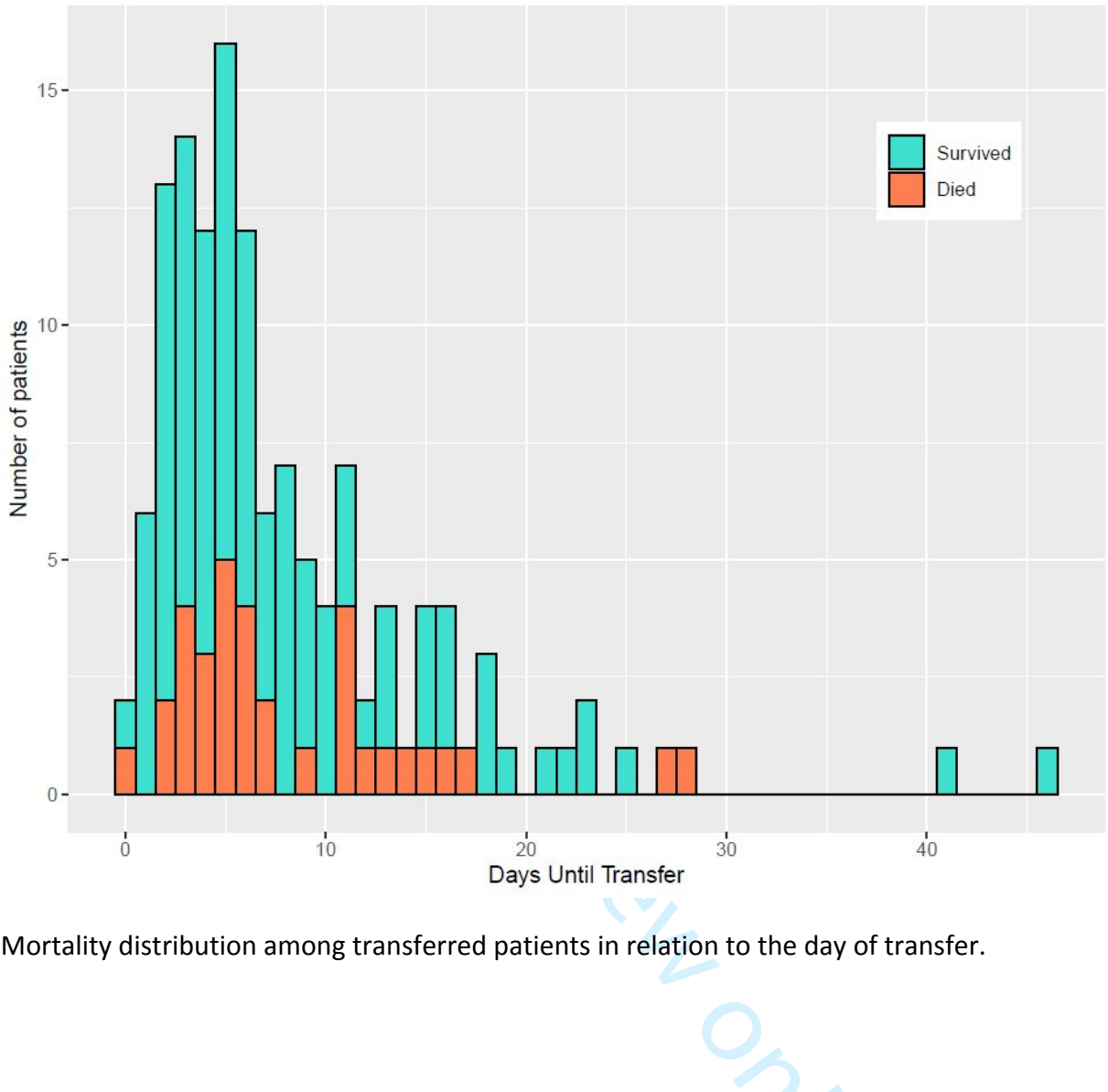
Figure 1. Flowchart of study inclusion







Supplementary File 1. Figure displaying 90-day mortality by ICU day of transfer



Mortality distribution among transferred patients in relation to the day of transfer.

Supplementary File 2. Subgroup analysis regarding mechanical ventilation and treatment limitations.

For the group without mechanical ventilation (total 321, 319 without IHT and two with IHT), neither of the two patients with exposure to IHT died within either 30 or 90 days compared to the 66 patients (21%) in the group without mechanical ventilation in the group not exposed to IHT. Due to the small number of patients and no event in the group without mechanical ventilation and IHT, the analyses were neither of interest nor statistically appropriate. When analysing only the subgroup of patients with mechanical ventilation (total 344, 213 without IHT and 131 with IHT), the results showed a reduced risk of death in both the univariate model, HR 0.51 (95% CI 0.32–0.81) for 30-day mortality and HR 0.60 (95% CI 0.40–0.89) for 90-day mortality, and the multivariate model, HR 0.40 (95% CI 0.25–0.65) for 30-day mortality and HR 0.45 (95% CI 0.30–0.68) for 90-day mortality.

For the group with treatment limitations (total 83, 78 without IHT and five with IHT), three patients (60 %) with exposure to IHT died within 30 and 90 days compared to the 55 (66%) and 58 (70%) with no exposure to IHT in 30 and 90 days, respectively. Even though the percentage was about the same in the two groups, the analysis was not carried out due to the small number of patients exposed to IHT with treatment limitations. For the patient group without treatment limitations (total 582, 454 without IHT and 128 with IHT), the results were the same as in the original models, showing no difference between patients without exposure to IHT compared to patients with exposure in the univariate model, HR 0.92 (0.58-1.48) for 30-day mortality and HR 1.08 (95% CI 0.72–1.60) for 90-day mortality, and a difference in the multivariate model, HR 0.38 (95% CI 0.23–0.62) for 30-day mortality and HR 0.45 (95% CI 0.29–0.68) for 90-day mortality.

Supplementary File 3. Characteristics of mechanically ventilated patients

Characteristics of mechanically ventilated patients admitted to an ICU for SARS-CoV-2 (non-invasive ventilated patients were excluded)

	All patients	Non-IHT patients	IHT patients	p-value
Total number (%)	344	213	131	
Age, median (IQR)	64 (55–71)	64 (55–71)	65 (57–72)	ns
Sex, n (%)				ns
Men	258 (75)	157 (74)	101 (77)	
Women	86 (25)	56 (26)	30 (23)	
BMI, n (%)	(n=341)	(n=210)		ns
>30	139 (41)	89 (42)	50 (38)	
<30	202 (59)	121 (58)	81 (62)	
SAPS 3, median (IQR)	57 (53–63)	57 (53–63)	57 (53–63)	ns
CCI category, n (%)				ns
0	132 (38)	82 (39)	50 (38)	
1	133 (39)	81 (38)	52 (40)	
≥2	70 (23)	50 (23)	29 (22)	
Limitations on life-sustaining treatments, n (%)				ns
Yes	16 (5)	11 (5)	5 (4)	
No	328 (95)	202 (95)	126 (96)	
COVID-19 period, n (%)				0.003*
Wave 1	160 (47)	113 (53)	47 (36)	
Waves 2–3	184 (53)	100 (47)	84 (64)	

Abbreviations: BMI: body mass index; SAPS 3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index score; SD: standard deviation; ns=no statistically significant differences, *p<0.05 statistically significant differences.