Impaired oxygenation and hemodynamic instability are independent predictors of long-term mortality in a regional cohort needing urgent fixed-wing intensive care transport to tertiary care

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Abstract

Background We aimed to test if impaired oxygenation or major hemodynamic instability at the time of emergency intensive care transport between hospitals are predictors of long-term mortality.

Methods From a regional hospital intensive care transport research database, the study cohort was identified as those emergency intensive care cases transported in fixed-wing air ambulance from outlying hospitals to a regional tertiary care center during 2000–2016 for adults (16 years old or older). Impaired oxygenation was defined as oxyhemoglobin % - inspired oxygen fraction ratio (S/F ratio) < 100. Major hemodynamic instability was defined as need for treatment with noradrenaline infusion to sustain mean arterial pressure (MAP) at or above 60 mmHg or having a mean MAP < 60. All-cause mortality at 3 months after transport was the primary outcome, and secondary outcomes were all-cause mortality at 6 and 12 months. Multivariate cumulative survival and hazard analysis was performed for intervals 3, 6 and 12 months.

Results There were 2142 patients included in the analysis. The S/F ratio < 100 was associated with increased mortality risk compared to S/F > 300 at all time-points, with hazard ratio (HR) 2.9 (1.9–4.4 95% CI, $p < 0.001$) at 12 months. Major hemodynamic instability during ICU transport was associated with increased HR of all-cause mortality up to one year with hazard ratio 1.9 (1.5–2.5, $p < 0.001$).

Conclusion Major impairment of oxygenation and/or major hemodynamic instability at the time of ICU transport to get to urgent tertiary intervention is strongly associated with reduced survival at least up to one year after the transport, in this cohort. These findings support the conclusion that these conditions are markers for many fold increase in risk for death notable already at 3 months after transport for patients with these conditions. How much this risk is modifiable is not assessable in this analysis.

Background And Aims

For sparsely populated regions in high income countries, advanced specialty and subspecialty care is often centralized to larger hospitals. This means that when patients become critically ill, and then need highly specialized care which is only available in regional tertiary and quaternary hospitals, they need to be transferred urgently to these regional centers. When distances are great between hospitals, this transport is most efficiently managed by an air ambulance system adapted for providing critical care during transport. For longer distance transports, fixed-wing ambulance systems are more cost-effective than helicopter emergency medical systems. (1) Inter-hospital critical care transports in northern Sweden are carried out by specialized teams of anesthesiology/intensive care physicians and nurses, and the fixed-wing air ambulance critical care transport system is based at the University Hospital of Umeå(2).

Critically ill patients often suffer from a range of physiological derangements, which require advanced medical management during the transport, but also might contribute to risk for reduced later survival. Impaired gas exchange in the lungs leading to end-organ stress or injury is common amongst critically ill patients. A hypoxemic tendency can be seen in up to 15 % of those who arrive to hospital after air ambulance transport(3). Endotracheal intubation and mechanical ventilation may improve oxygenation at the time of transport, but hypoxemia is still seen in up to 3 % at arrival to hospital(4,5). Circulatory disturbances are also common, and are often present at the same time as hypoxemia, which is associated with higher mortality(6). Up to 10 % of patients may be hypotensive when arriving to hospital with air ambulance(5).

We hypothesized that impaired oxygenation and major hemodynamic instability both independently are associated with increased risk for all-cause mortality at 3 months. A secondary hypothesis is that the same would be associated with increased risk all-cause mortality up to 12 months after transport.

Methods

Study population

This retrospective observational study was conducted with ethical approval from the Swedish Ethical Review Authority (Dnr 2019-06525). The anonymized study cohort database was generated from the Departmental (air ambulance) patient registry for critically ill patients undergoing fixed-wing air ambulance transportation to the University Hospital of Umeå, and linkage to date of death data from the Swedish National Board of Health and Welfare. Inclusion was for all cases during 2000-2016 for ages 16 years or older from missions originating from local hospitals in the northern healthcare region of Sweden to take patients emergently for more definitive care at the regional tertiary care center. Exclusion criteria included the following: cases with transport solely for organ transplantation purposes, missing data (n=6 for major hemodynamic instability), non-urgent transports, patients without a Swedish personal identity number (not in the national citizen registry).

Setting

The Swedish northern healthcare region consists of the four northern-most counties of Sweden; Norrbotten, Västerbotten, Västernorrland and Jämtland, which make up a total of approximately 900 000 inhabitants over 210 000 square kilometers, where each county has smaller hospitals. The fixed-wing ICU transport system at the regional tertiary facility, the University Hospital of Umeå have teams that are active around the clock, every day, to provide rapid response times for emergency ICU patient transports. Transport logistics are coordinated centrally, including road ambulance between hospitals and airports.

Data

Case factors included in the analysis are age, sex, diagnostic group, total transport time, mode of breathing (for example endotracheal intubation), and physiological data such as blood pressure, heart rate and oxygen saturation measured by pulse oximetry (SpO_2). To assess oxygenation status amongst the patients where there were simplified ventilator FiO_2 (fraction of inspired oxygen) settings during transport as well as limited blood gas data during transport, the ratio of pulse oximetry oxyhemoglobin percent and inspired oxygen fraction (SpO_2/FiO_2, S/F) was used. The threshold for defining the impaired oxygenation category (S/F <100) degree of oxygenation impairment was chosen with support from the Berlin criteria for ARDS(7). The definition of major hemodynamic instability as a binary outcome was where noradrenaline infusion was implemented to achieve a MAP > 60 mmHg or a mean MAP <60 mmHg.

Outcomes

The primary outcome was all-cause mortality at 3 months after their emergency inter-hospital ICU transport. Secondary outcomes were all-cause mortality at 6 and 12 months.

Statistical analysis

Statistical analysis was carried out using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Power analysis was carried out on the expected sample size of 2000 patients (PASS 15 Power Analysis and Sample Size Software 2017. NCSS, LLC. Kaysville, Utah, USA). A power of 93 % with 0.05 significance was calculated based on 200 people in exposed and unexposed groups, with a presumed hazard ratio of 2. Shapiro-Wilks test was used to assess normal distribution, after which for non-normally distributed data, the non-parametrical Mann-Whitney U test was used to test the null hypothesis with ordinal/continuous data. Chi square and Fisher's exact test was used for nominal data. Logistic regression was used to estimate mortality risk (OR) for different levels of oxygenation and circulatory disturbances. Cox regression was used to study cumulative mortality at specific time points in the different physiological states. Adjustments for sex and age in the regression model were included where indicated, and relative risks are presented with 95% confidence intervals. Adjustment of age was made since this is a known confounder in mortality studies both regarding intensive care and inter-hospital transportation. The adjustment for sex was made due to a majority of cases being male. Complete case analysis was used, so there were no missing values for S/F ratio and all-cause mortality data. Missing values for major hemodynamic instability (n=6) led to cases being omitted from analysis.

Results

There were 3917 unique cases identified in the database, of which 1775 did not meet inclusion criteria (Fig 1), providing 2142 cases for further analysis. In the analysis for major hemodynamic instability, 20 cases were excluded for incomplete data, leaving 2122 cases for that analysis.

Characteristics of the cohort

Patient characteristics show a higher proportion of males (64.3%) (Table 1). The most common diagnostic group being heart-lung conditions (38.9%) followed by neurological and neurosurgical conditions. The mean age was 57.6 years old with the youngest being 16 and the oldest being 96 years. Most patients spontaneously maintained a mean MAP > 60 (78.6%), and did not require noradrenaline infusion (83.9%). Almost 13% had tachycardia (heart rate >100 beats per minute) and 4.9% a systolic blood pressure (SBP) < 90 mmHg. The most commonly observed S/F ratio was >300 (n=67.3%).

Table 1. Characteristics of the cohort

Sex*	Male	Female			
	1379 (64.3)	764 (35.7)			
Median age**	57.6 (15.1-95.6)				
Diagnostic groups*	Heart-lung	Surgical	Neuro	Infectious	Internal medicine
	833 (38.9)	608 (28.4)	610 (28.5)	50 (2.3)	42 (2.0)
SpO2/FiO2*	< 100	101-200	201-300	>300	
	25 (1.2)	540 (25.2)	135 (6.3)	1142 (67.3)	
MAP < 60 mmHg*	Yes	No			
	6 (0.3)	1732 (78.6)			
SBP < 90 mmHg*	Yes	No			
	108 (4.9)	1835 (83.3)			
Heart rate > 100 bpm*	Yes	No			
	285 (12.9)	1905 (87.0)			
Noradrenaline infusion*	Yes	No			
	333 (15.1)	1850 (83.9)	-	-	-

MAP=Mean arterial pressure; SBP=Systolic blood pressure.
Values are * number of patients (percentage) or ** median (range)

Impaired oxygenation

The main findings for the lowest oxygenation group (S/F<100) was that there was an increased HR for mortality over the first 3 months after the ICU transport, as well as at 6 and 12 months, compared to the normal oxygenation group (S/F>300) (Table 2). After adjusting for sex and age, the HR for mortality was 5.1 (2.5-10.5, $p<0.001$) at 3 months. Secondary findings at 6 and 12 months showed adjusted HR of 4.7 (2.4-9.3, $p<0.001$) and 4.0 (2.0-7.8, $p<0.001$) respectively. The HR for mortality was also higher in the S/F 101-200 and S/F 201-300 group, compared to S/F>300, albeit lower than in the S/F<100 group (Table 2), supporting the idea of a ‘dose effect’ of impaired gas exchange on mortality. Crude (Fig S1A) as well as sex- and age-adjusted cumulative survival plots (Fig 2A) demonstrate these findings. Cumulative survival for the S/F>300 group at 12 months was 89% whereas it was 64% in the S/F<100 group, while being 78% and 76% in the S/F 101-200 and 201-301 groups.

Table 2. COX regression of different degrees of oxygenation and mortality.

	Crude HR (95 % CI, p value)	Adjusted for sex and age HR (95 % CI, p value)
3 months		
S/F <100	4.7 (2.3-9.6, p<0.001)	5.1 (2.5-10.5, p<0.001)
S/F 101-200	2.5 (1.9-3.2, p<0.001)	2.9 (2.2-3.8, p<0.001)
S/F 201-300	2.9 (1.9-4.4, p<0.001)	3.1 (2.0-4.7, p<0.001)
S/F>300 reference		
6 months		
S/F <100	4.4 (2.2-8.6, p<0.001)	4.7 (2.4-9.3, p<0.001)
S/F 101-200	2.3 (1.8-2.9, p<0.001)	2.7 (2.1-3.5, p<0.001)
S/F 201-300	2.6 (1.8-3.9, p<0.001)	2.8 (1.9-4.2, p<0.001)
S/F>300 reference		
12 months		
S/F <100	3.7 (1.9-7.3, p<0.001)	4.0 (2.0-7.8, p<0.001)
S/F 101-200	2.1 (1.7-2.7, p<0.001)	2.5 (2.0-3.2, p<0.001)
S/F 201-300	2.4 (1.7-3.5, p<0.001)	2.6 (1.8-3.8, p<0.001)
S/F>300 reference		

Major hemodynamic instability

The main finding for major hemodynamic instability was associated with an increased HR of mortality in the adjusted model, with HR 2.4 (1.8-3.3, p<0.001) at 3 months. Secondary findings at 6 and 12 months showed for hemodynamic instability an adjusted model HR of 2.2 (1.7-3.0, p<0.001) and 2.0 (1.5-2.7, p<0.001) respectively. There is a clear difference in cumulative survival between the groups in both the crude (Fig S1B) and adjusted model (Fig 2B). The separation grows with time post-transport, with 76% cumulative survival at 12 months for cases with major hemodynamic instability during transport, and 84% cumulative survival for cases who did not have hemodynamic instability

Simultaneous impaired oxygenation and major hemodynamic instability

There were only 13 cases where both of these exposures were present in the same case, and these demonstrated a hazard ratio which was in between the factor subgroups (Table S1). The increased risk, when adjusted for sex and age, was HR 3.0 (1.1-1.8, p=0.029), 3.2 (1.3-7.8, p=0.009) and 2.9 (1.2-6.9, p=0.019) at 3, 6 and 12 months post transport.

Table 3. COX regression of major hemodynamic instability and its influence on mortality.

	Crude HR (95 % CI, p value)	Adjusted for sex and age HR (95 % CI, p value)
3 months		
Present	2.3 (1.7-3.0, p<0.001)	2.4 (1.8-3.2, p<0.001)
Absent		
6 months		
Present	2.1 (1.6-2.8, p<0.001)	2.2 (1.7-2.9, p<0.001)
Absent		
12 months		
Present	1.9 (1.5-2.5, p<0.001)	2.0 (1.6-2.6, p<0.001)
Absent		

Discussion

In this retrospective cohort analysis, long-term mortality risk is quantified for both impaired oxygenation and major hemodynamic instability at the time of fixed-wing emergency air ambulance ICU transport. The main finding is that the mortality risk within 90 days is particularly high for major oxygenation impairment, approximately 5 times, that of those who had no oxygenation impairment. The mortality risk for circulatory instability for the same time period is also approximately doubled compared to those not demonstrating circulatory instability. This impact on survival is despite early and aggressive intensive care. In this analysis, it is not possible to separate contributing risk of co-morbidity or factors before the critical care and transport episode, something that might be a significant contributor to mortality both in air ambulance transportation and in the ICU(8–11). The relative mortality risks for cases with these conditions is in general agreement with those presented in some recent reports for shorter distance, rotary-wing ambulance, primary transports with ICU character(4,12).

The cases in this cohort were transports initiated based on acute illness or injuries which occurred to get from initial resuscitation at a local hospital in a sparsely populated region, to tertiary or quaternary care at the regional university hospital. In this, there was an inevitable time interval between critical illness debut and implementation of some forms of specialty care, including specialty interventions in the university hospital. Still, there was always advanced general intensive care provided at the local hospital. The transport step also involved best possible provision of the same level of intensive care during the transfer from local to university hospital, although with crude ventilator settings (FiO2 1.0 or 0.6) and no possibility to assess arterial blood gas. Significant mortality risk is associated with different conditions at the start of need for critical care, including for example different forms of shock(13–16).

The quantification of the exposures here, respiratory and circulatory impairment, were chosen based on the available physiological data recorded in the patient records. It would have been optimal to have serial blood gases and close adjustments in ventilatory parameters to be very precise about alveolar-arterial oxygen gradients, but these were not generally available for this cohort. The S/F index(17,18) was available for all cases, and provided for reliable separation of these cases with highly impaired lung gas exchange for oxygen, as well as for those with no oxygenation impairment. The S/F groups in-between may be less precise or crude as far as for quantifying oxygenation, but still an apparent dose effect of oxygenation impairment was demonstrated in the mortality risk analysis for these middle ranges. Concerning impaired circulation, further corroborating measures of inadequate circulation would have helped to confirm precision in this grouping. Noradrenaline infusion treatment may have been present for some cases for different reasons: for inadequate fluid resuscitation, for counter-acting sedative-related blood pressure effects, or for other reasons. It was chosen, along with observed low MAP, as a category with this understanding that there might be a number of cases included in the group which were not due to primary circulatory insufficiency, but still had a noradrenaline infusion, which would dilute the results related to those with true shock. The possible effect of this on the analysis would be to underestimate the effect of hemodynamic instability as observed here on mortality.

The absolute mortality rate within 90 days of transport in the most impaired oxygenation group (S/F<100) was approximately 25%. This can be appreciated together with what is widely recognized as the high mortality risk associated with ARDS(19,20). These were not cases of ARDS, at least at the time of transport. This relative risk analysis was based only on clinical conditions at the time of transport, which was at the beginning of the hospitalization period.

Conclusion

In summary, this cohort analysis has quantified relative mortality risks related to these two conditions in cases at the point of emergent long-distance critical care transport in the start of an intensive care treatment period. From these findings, we conclude that major impairment of oxygenation and/or major hemodynamic instability at the time of ICU transport in this setting is strongly associated with reduced survival at least up to one year after the transport. These conditions may be markers for this many-fold increase in risk for death notable already at 3 months after transport. How much this risk is modifiable is not assessable in this analysis.

List Of Abbreviations

PaO2- partial pressure of oxygen, FiO2- fraction of inspired oxygen, SpO2- peripheral oxygen saturation, S/F ratio - SpO2/FiO2 ratio, MAP- mean arterial pressure, SBP- systolic blood pressure, ARDS- Acute Respiratory Distress Syndrome, ALI- Acute Lung Injury, PEEP- Positive End-Expiratory Pressure, CPAP- Continuous Positive Airway Pressure, ICU- intensive care unit.

Declarations

Ethics approval and consent to participate

Ethical approval has been granted by the Swedish National Research Ethical Review authority (document number 2019-06525, Ethical review board chairman Peter Strömberg). The data has been anonymized prior to processing with original patient record access only made available to the primary investigator.

Consent for publication

This is not relevant since no individual patient can be identified.

Availability of data and materials

The datasets analyzed can be made available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

- MFS contributed to the planning, data collection and analysis, and the writing and approval of the final manuscript.

-AS contributed to the planning, data collection and analysis, and the writing and approval of the final manuscript.

-EL contributed to the planning, data collection and analysis, and the writing and approval of the final manuscript.

-HN contributed to the planning, and the writing and approval of the final manuscript.

-GJ contributed to the planning, data collection and analysis, and the writing and approval of the final manuscript.

-HB contributed to the planning, data collection and the writing and approval of the final manuscript.

-MH contributed to the planning, data collection and analysis, and the writing and approval of the final manuscript.

All authors read and approved the final manuscript.

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Figures

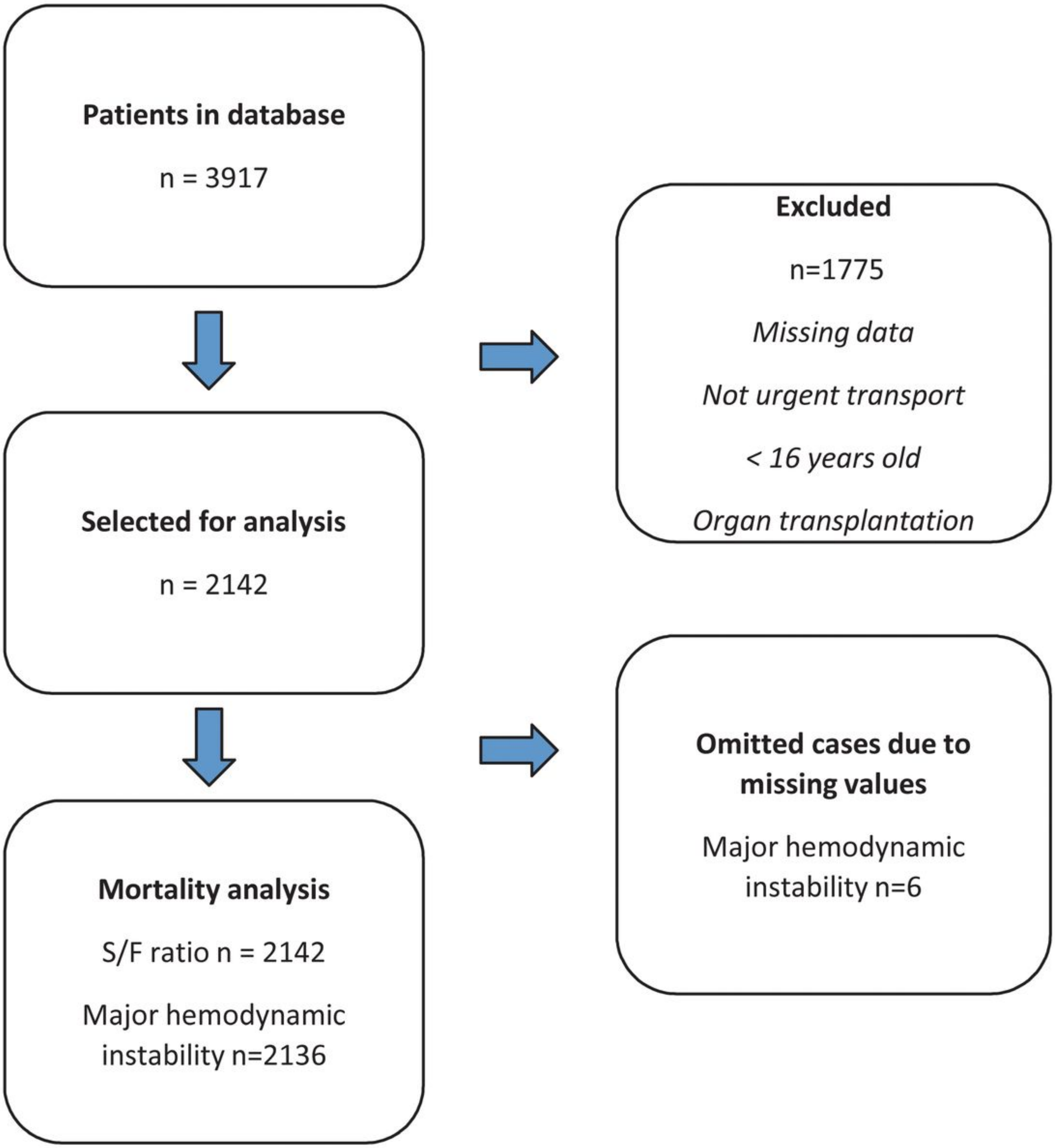

Figure 1

Flowchart of patient selection for this study

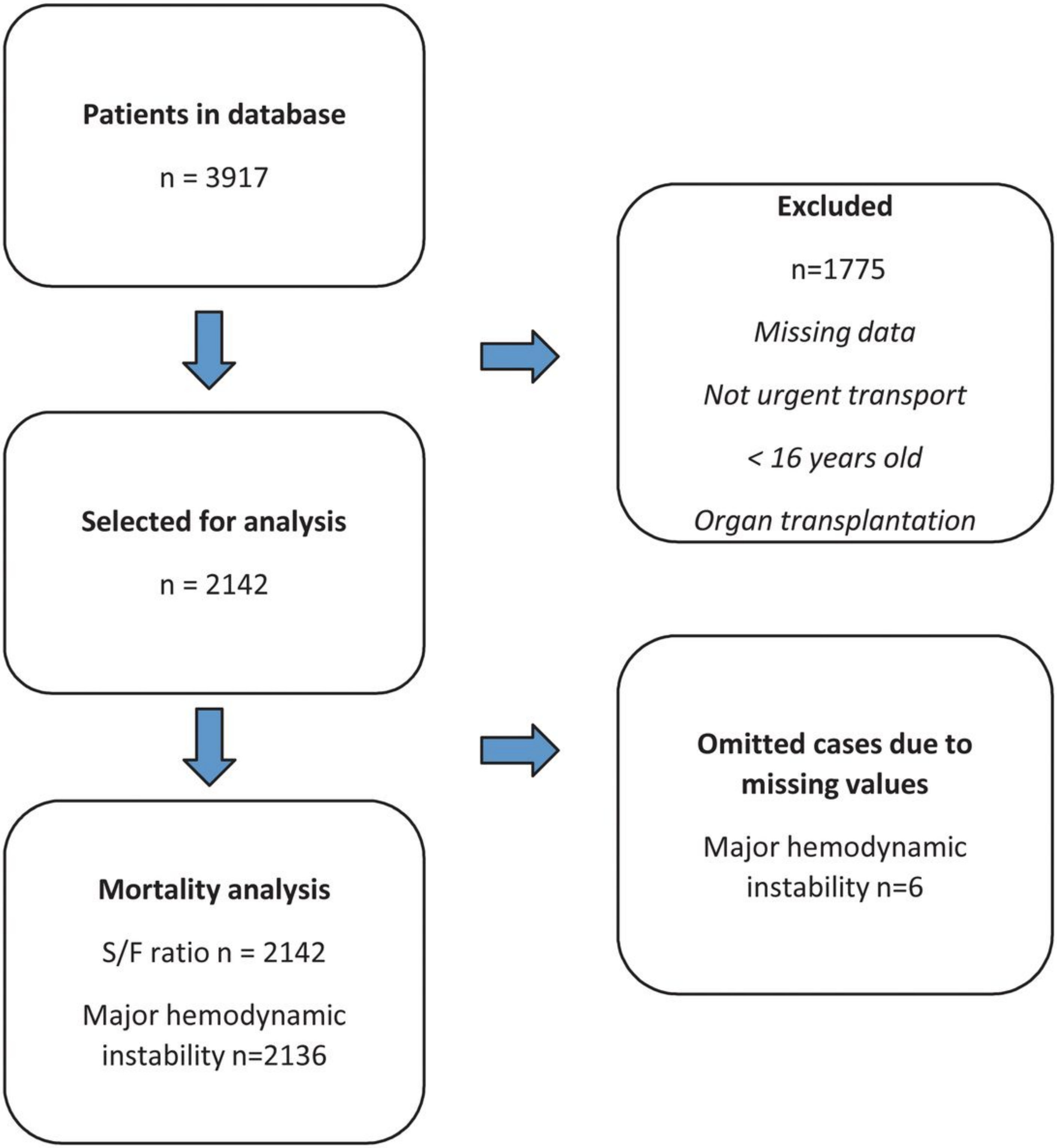

Figure 1

Flowchart of patient selection for this study

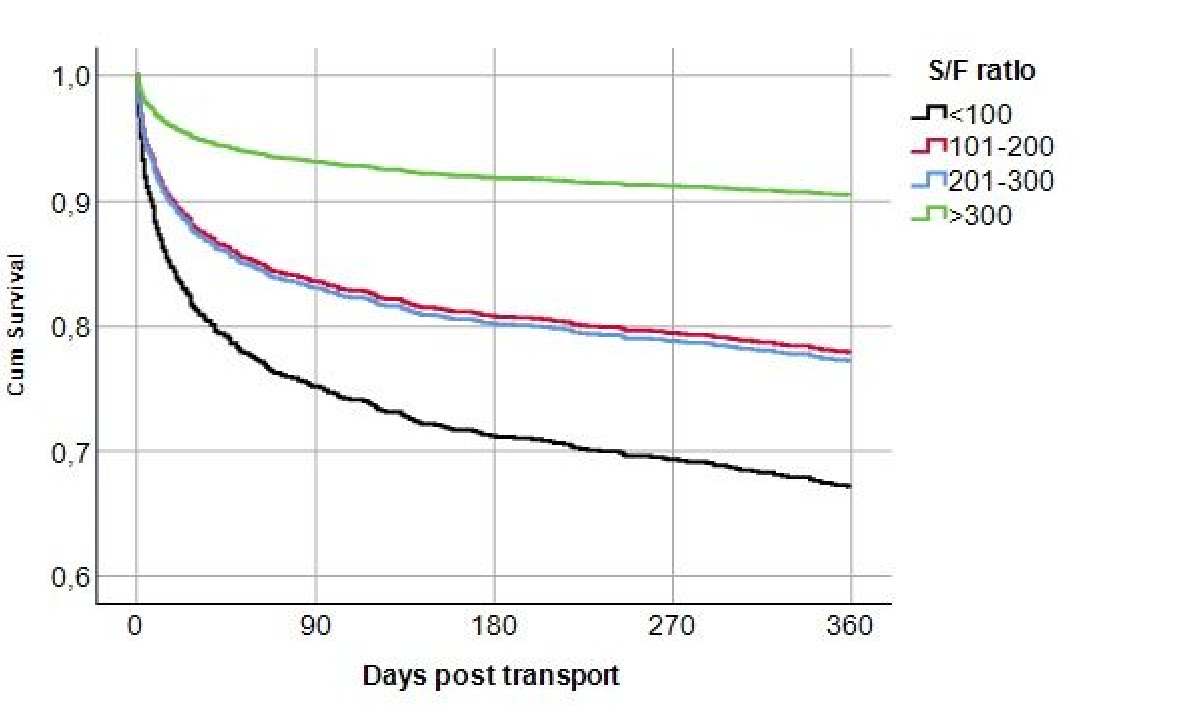

Figure 2

Cumulative survival in impaired oxygenation and major hemodynamic instability Sex and age adjusted. Upper panel: Different SpO2/FiO2 ratios and cumulative survival up to 12 months, n=2142. Lower panel: Presence or absence of major hemodynamic and cumulative survival up to 12 months, n=2136.

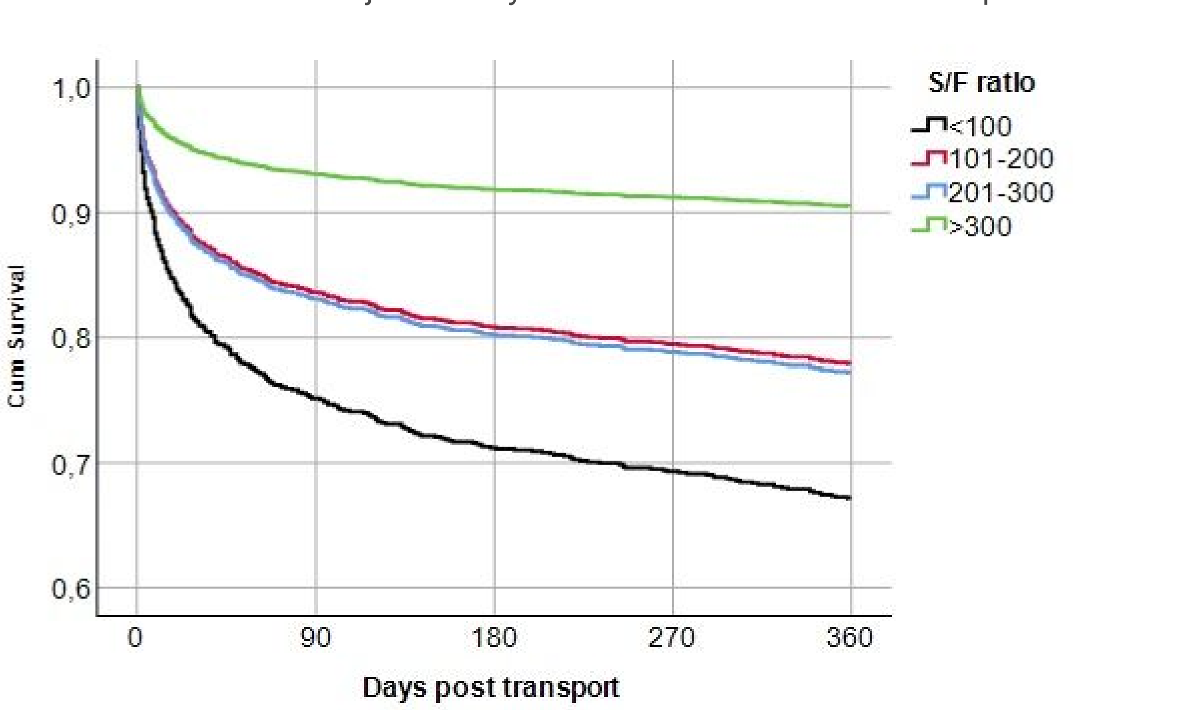

Figure 2

Cumulative survival in impaired oxygenation and major hemodynamic instability Sex and age adjusted. Upper panel: Different SpO2/FiO2 ratios and cumulative survival up to 12 months, n=2142. Lower panel:

Presence or absence of major hemodynamic and cumulative survival up to 12 months, n=2136.

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