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Abstract

Blood group has been found to be important in the development of many diseases and the outcome of several disease processes, especially cardiovascular morbidity and mortality, such as caused by trauma and sepsis. The main reason is claimed to be related to glycobiology and effects mediated through the endothelium. This study investigated the possible effect of bloodgroup (ABO) on burn care outcome. Burn outcome prediction models are extremely accurate and as such can be used to identify outcome effects even in single centre settings. In this retrospective risk adjusted observational study, we investigated the effect of ABO blood group on ventilatory time, length of hospital stay (LOS), and 90 day mortality among patients with burns.

Results. A total of 225 patients were included (2008-2019) with median TBSA of 26%; interquartile range (IQR) of 20%–37%; median age 45 years (IQR 22–65 years); median Baux score (age + TBSA%); 76 (IQR 53– 97); 168 (75%) were male; median duration of hospital stay was 31 days (IQR 19–56); a total of 138 (61%) received treatment with mechanical ventilation; and 29 (13%) died. In a multivariable regression model, we were unable to isolate any significant effect of any blood group (O, A, B, AB) on the outcome measures studied (ventilatory time, LOS, and mortality).

In summary, contrary to many other major areas of disease in which ABO blood groups affect outcome, we were unable to find any such effect on patients with burns. Given the precision of the outcome models presented (AUC 0.93) any such an effect, if missed due to the limited study cohort, may be considered limited and to have only a minor clinical impact.

Key words: ICU, Large burns, Mortality prediction, Survival, Total Body Surface area burned (TBSA %)

Introduction

Since 1901, when Landsteiner identified ABO as the first recognised human blood grouping system, its biological and clinical importance has been extensively documented. The clinical significance of ABO blood typing is important and to date numerous reports have suggested associations between ABO blood groups and various diseases [1]. Its role in cardiovascular disease has been particularly underlined and reviewed [2]. In this context, the underlying mechanisms have been claimed to be related to glycobiology and the interaction with the endothelium [3]. Similarly, blood group O has been associated with a lower risk of getting COVID-19 infection and blood group A with a higher mortality in COVID-19 infection [4, 5]. Furthermore, a higher risk of developing gastric carcinoma has been associated with blood group A [6]. This relation has been claimed to be important both scientifically and for translational purposes [1]. Recently, focus has also been directed towards the possible effects and implications of the ABO system for critical illness and survival [7-9]. The underlying mechanism is mediated locally in the vasculature and the inflammatory processes [10]. In this context, both sepsis- and trauma-induced Acute Respiratory Distress Syndrome (ARDS) [10], and acute kidney injury (AKI) [7] seem to be affected by the ABO factors as well as direct outcomes related to trauma [7-9]. However, in contrast, investigators were unable to find a correlation between ABO blood type with ICU mortality and ICU length of stay (LOS) in adult patients with acute hypoxaemic respiratory failure who were mechanically ventilated [11].

In the critical care setting when examining the effects of blood group, it is important to properly make risk adjustments to be able to identify and isolate such outcome effects. From this perspective, the risk adjustment models in burns critical care are well known for their high precision [12]. A recent publication reported that blood group O was an independent factor for increased mortality among severe burns after adjustment for age, burn size, and depth, but they found no effect on hospital stay or intensive care stay [13]. Therefore, we aimed in this study to examine if we could confirm the effect of the ABO system on hospital length of stay, ventilatory time, and burn mortality.

Method

All patients admitted during 2008–2019 for burns ≥ 15% total body surface area (TBSA) were included. Mortality was defined as death within 90 days after injury. Patients who were treated with comfort care early after admission were excluded as well as patients lost to follow up at 90 days after injury. Data were collected retrospectively from the medical records, and from prospectively recorded burn-specific data entered in the local computerised burn registry [14]. Patients were treated according to our usual protocol, including early excision and grafting [15], standard ventilation, early enteral nutrition, and laboratory assessment according to thelocal guidelines. Different aspects of this have been previously described [16, 17]. Burn size TBSA% and depth was recorded on admission using a detailed Lund and Browder chart.

Ethical Approvals

The study was approved by Linkoping Regional Ethics Review Board. (No. 2013\341-31)

Statistics

Data are presented as median (25^{th}–75^{th} centiles), unless otherwise stated. Differences between groups were analysed using the Kruskal-Wallis ANOVA, Mann–Whitney U, and the chi squared test. Multivariable regression was used to analyse the effect on mortality (logistic) and duration of hospital stay and days on mechanical ventilation (linear), adjusted for age, burns size and depth, treatment with mechanical ventilation (yes coded 1, no coded 0, as an indicator of smoke inhalation: patients with chemical injuries, scalds, and contact injuries were coded as "no mechanical ventilation" when used as independent variable in the regressions), and number of operations and units of concentrated red blood cells transfused. The regressions for hospital stay and number of days on mechanical ventilation was done only on patients who survived. Data were analysed with the help of STATA (STATA v12.0, Stata Corp. LP College Station, TX, USA). Probabilities of less than 0.05 were accepted as significant.

Results

A total of 252 patients were admitted, 15 were treated with comfort care early after admission, 12 were lost to follow up, and the final study group included 225 patients: median TBSA was 26%; with interquartile range (IQR) of 20%–37%; median age was 45 years (IQR 22–65 years); median Baux score (age +TBSA%) was 76; (IQR 53– 97); 168 (75%) were male; median duration of

hospital stay was 31 days (IQR 19–56); a total of 138 (61%) received treatment with mechanical ventilation; and 29 (13%) died. Details of the patients grouped by blood type are presented in Table 1, while Table 2 shows details of those who survived or died.

Mortality

Simple logistic regression with blood type coded as categorical (O, A, B, AB) showed no tendency of higher crude mortality for any blood type (Table 3, simple regression). As the number of patients were few in blood types AB and B, we also tested each blood type against the others, but no further associations could be detected. Logistic multivariable regression showed that age, the size of deep dermal and full thickness burns, and treatment with mechanical ventilation, number of operations and units of red blood cells transfused were independent variables for 90 day mortality while the contribution of blood was not significant (Table 4), and neither was the contribution to the ROC AUC value of 0.93 (95% CI 0.89 to 0.97) by adding blood type to the model (p=0.24) (Fig. 1, **SUPPORTING INFORMATION**).

Hospital length of stay

Linear simple regression for duration of hospital stay among the patients who survived showed no associations with blood type (Table 5). Also, in this analysis we tested all blood types as reference, and each blood type against the others,but no associations could be detected. Linear multivariable regression showed that age, the size of deep dermal and full thickness burns, number of operations and red blood cell transfusions, were independent variables for duration of hospital stay, while the contribution of blood type was not significant (Table 6).

Days on mechanical ventilation

Linear multivariable regression for number of days on mechanical ventilation among the patients who survived showed that age, burn size of all depths, and number of operations were independent variables for the duration of treatment with mechanical ventilation, while the contribution of blood type was not significant (Table 7).

Discussion

In this retrospective registry cohort investigation of ABO blood group effects on burn care

outcomes, we were unable to find any such correlation to length of stay, ventilatory time, and mortality. This contrasts with previous studies addressing ICU care-related outcomes such as those after trauma [7-9], and sepsis [7]. It also deviates from studies addressing infectious complications [4, 5] but is in line with the findings presented on ICU mortality and LOS in acute hypoxaemic respiratory failure [11]. Yao et al. found a considerable effect of blood type O on mortality after severe burns, the coefficient was 1.42 (p=0.02) in a regression adjusted for age, burn size, and depth, calculated on 114 patients with a median burn size of 70% TBSA and an in-hospital mortality of 23% [13]. The corresponding effect (blood type O compared to the other) was in the same direction in our study but smaller (coefficient 0.80) and not significant (p=0.15) although our study group was bigger. It is thus possible that there can be an effect among the most severe burns, yet further studies from centres bigger than ours are needed to determine this.

In a recent rather extensive study performed on a large cohort in Sweden [1], the authors were able to depict 1217 disease categories related to ABO blood groups, included in 70 million person-years follow up in 5.1 million individuals. Interestingly, in this study we recorded the following findings, that we believed could be important for burn care, such as increased infection rates (erysipelas, pneumonia), coagulation defects in general, diabetes type 1 and 2, cardiovascular disease (myocardial infarct/heart failure), and vascular diseases both in the veins and arteries. All of these were found to be more prevalent in non-O blood groups, i.e., A, AB, and B. Despite all these correlations that would support an effect in the burn cohort, we were unable to register a correlation between any ABO blood group and any of the burn ICU care outcome (LOS, ventilatory time, and mortality).
The blood groups (ABO) amongst the patients in the burn cohort were distributed as anticipated from the literature in Sweden [1]. Having said this, it underlines that some of the blood groups, especially AB but also B, have even fewer observations, which makes the effectcaused by them very difficult, or impossible, to depict. On the other hand, the two most interesting blood groups from a documented outcome perspective are the A and O, as each presented with more than 80 observations in the present study.

Comparing our study with mainly the study that showed an effect (ARDS) of blood group in both a trauma and sepsis cohort by Reilly et al. [8], the trauma group consisted of 732 patients and 976 were sepsis and the corresponding rates for ARDS were 27% and 23%, respectively, (to be

compared to a similar relative effect variable in our study, i.e., mortality of 13 %). Then it needs to be emphasised that: first the effect observed by Reilly et al. [8] was in the white population, which only constituted 50% of the total population reaching an observed population even more like our study. Further, the risk adjustment techniques for two cohorts, in the Reilly study [8], were injury severity score (ISS) and APACHE III, which are both known to have significantly less predictive power than the variables (age and burn size) as used in this study [12].

ARDS as an outcome variable for the trauma and sepsis cohorts in the Reilly study [8] may further be considered relevant for the effect of variable ventilatory time as used in the present study. This, as it is known that ARDS is common in burns and that it prolongs ventilation and ICU length of stay [17].

Examining the study, by Reilly et al. in trauma and sepsis patients that developed AKI [7], which is much like the ARDS study a similar reasoning may prevail. An increased AKI outcome was seen amongst the 229 trauma patients of European decent. In the corresponding sepsis cohort, the study was based on 277 patients. Both comparisons are similar to the present study in terms of numbers. It is also well documented that AKI is common in major burns at the unit of this study, and carries a significant mortality [18].

A strength of the present study is that the burn care process at this specific centre is well documented, has been constant during the study period, and the data collection procedure has been optimised by a yearly evaluation and a prospective recording approach [12, 14-18]. The outcome parameters (LOS, ventilatory time and mortality) have been repeatedly compared with other units in different parts of the world, especially high-income countries and Europe, and the outcomes have been comparable to other units, thus supporting a generalisability of the present findings in major burns [12, 14-18].

Limitations of the study

This study is a single centre burn ICU care study in a low-density population area of the world thus producing a limited study cohort. Having said this, concurrently the main risk is that there may have been a blood-related effect of the ABO blood group on burn care outcome in the ICU, but that this effect had passed undetected. When addressing this issue, it is important to note that the burn care ICU prediction model has a strong predictive power, as e.g., based on the AUC

value of more than 0.90 as is presented in this study. But then it needs to be stressed that even though the sensitivity is high the specificity is significantly lower and thus the risk of missing a blood group effect is increased. When comparing the other outcome measures that were studied, such as age and effects of burn size and depth, it needs to be appreciated that the 95% confidence intervals are similar to the ones produced by the model for the blood groups (ABO), thus supporting the theory that if there is an effect of the blood groups on burn care outcome, it may be assumed to be minor. The latter is further supported by the positive correlations seen in the previously cited ICU investigations [7, 8, 10], which have had odds ratios that were quantitatively small.

In conclusion, contrary to many other areas of major disease in which ABO blood groups affect outcome, we were unable to find any such effect on burn care outcome (LOS, ventilatory time, and mortality) in patients with burns. Given the precision of the outcome, models that have presented any such an effect, if missed due to the small study cohort, may be considered to be less significant and to have a limited clinical impact.

Conflict of Interest Statement

Neither of the authors declare a conflict of interest

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Table 1 – Details of the patients grouped by blood type

	O	A	B	AB	p-value
No. of patients[a]	85 (38)	96 (43)	36 (16)	8 (4)	
Age, years	48.0 (21.0–65.0)	42.5 (23.0–57.5)	51.5 (25.0–66.5)	32.5 (17.5–71.0)	0.63
Sex, male	60 (71)	72 (75)	32 (89)	4 (50)	0.07
Hospital stay, days	34.0 (21.0–64.0)	31.0 (18.0–47.0)	24.0 (17.5–51.0)	33.0 (26.0–56.0)	0.38
TBSA%:	29.0 (21.0–40.5)	24.4 (18.3–33.5)	26.0 (19.3–40.3)	30.0 (21.0–42.3)	0.16
Superficial dermal BSA%	2.0 (0.0–15.3)	4.3 (0.0–13.3)	3.3 (0.0–16.0)	8.5 (0.0–21.0)	0.97
Deep dermal BSA%	7.5 (2.5–20.5)	8.8 (2.5–18.0)	6.0 (0.3–14.8)	2.4 (0.6–11.5)	0.28
Full thickness BSA%	6.0 (0.0–16.5)	0.1 (0.0–12.8)	7.0 (0.0–22.5)	0.0 (0.0–23.3)	0.11
Mortality	14 (16)	9 (9)	5 (14)	1 (13)	0.56
Patients on mechanical ventilation	54 (64)	58 (60)	20 (56)	6 (75)	0.72
Patients on mechanical ventilation*	51 (60)	54 (56)	17 (47)	4 (50)	0.62
Operations	5 (2.0–8.0)	3.5 (1.0–7.0)	3 (1.0–6.0)	3.0 (1.5–5.5)	0.34
Red blood cell transfusion, units	19.0 (3.0–43.0)	11.0 (0.5–30.0)	7.5 (1.5–32.5)	9.0 (5.5–14.5)	0.19

Data are presented as n (%) or median (25^{th} and 75^{th} centiles). [a]Percent of 225. Kruskal-Wallis ANOVA and chi square test as appropriate. *Mechanical ventilation used as an indicator of smoke inhalation (patients with chemical injuries, scalds, and contact injuries were classified as “no mechanical ventilation” in this calculation).

Table 2 – Details of the patients grouped by survival status at 90 days after injury

	Survived	Died	p-value
No of patients	196 (87)	29 (13)	
Age, years	41.0 (21.0–58.0)	68.0 (63.0–73.0)	<0.001
Sex, male	150 (77)	18 (62)	0.09
Hospital stay, days	32.5 (20.0–56.0)	22.0 (5.0–48.0)	0.03
TBSA%	25.1 (19.3–36.0)	36.0 (25.0–43.5)	0.001
Superficial dermal BSA%	4.3 (0.0–15.9)	0.5 (0.0–2.0)	0.002
Deep dermal BSA%	7.0 (2.0–16.7)	17.2 (1.5–24.0)	0.10
Full thickness BSA%	2.0 (0.0–14.5)	18.0 (6.0–30.0)	<0.001
Baux score	71.9 (49.2–89.5)	109.0 (94.0–113.0)	<0.001
Patients on mechanical ventilation	109 (56)	29 (100)	<0.001
Patients on mechanical ventilation*	98 (50)	28 (97)	<0.001
Operations	4.0 (1.0–7.0)	5.0 (2.0–7.0)	0.36
Red blood cell transfusion, units	10.0 (1.0–31.0)	38.0 (17.0–50.0)	<0.001
Blood type			0.56
O	71 (36)	14 (48)	
A	87 (44)	9 (31)	
B	31 (16)	5 (17)	
AB	7 (4)	1 (3)	

Data are presented as median (25th and 75th centiles) or n (%). Mann-Whitney U and chi square test as appropriate.*Mechanical ventilation used as an indicator of smoke inhalation (patients with chemical injuries, scalds, and contact injuries were classified as “no mechanical ventilation” in this calculation).

Table 3 – Logistic simple regression for mortality

	Coefficient	p	OR	95% CI
O *(reference)*			1.00	
A	-0.65	0.16	0.52	0.21–1.28
B	-0.20	0.72	0.82	0.27–2.47
AB	-0.32	0.77	0.72	0.08–6.36
Constant	-1.62	<0.001	0.20	0.11–0.35

Model pseudo R^2 = 0.01, p= 0.55, ROC AUC 0.58 (95% CI 0.47–0.68).

Table 4 – Logistic multivariable regression for mortality

	Coefficient	p-value	OR	95% CI
Age, years	0.10	<0.001	1.10	1.05–1.16
Superficial dermal BSA%	0.02	0.49	1.02	0.96–1.08
Deep dermal BSA%	0.07	0.001	1.07	1.03–1.12
Full thickness BSA%	0.09	0.005	1.09	1.03–1.16
Mechanical ventilation*	2.68	0.02	14.64	1.56–137.58
Red blood cell transfusions	0.02	0.09	1.02	1.00–1.05
Operations	-0.40	0.003	0.67	0.51–0.87
Blood type:				
O *(reference)*			1.00	
A	-0.96	0.12	0.38	0.11–1.28
B	-0.20	0.82	0.82	0.15–4.40
AB	-1.63	0.43	0.20	0.00–11.41
Constant	-10.37	<0.001		

Model pseudo R^2 = 0.47, p<0.001, ROC AUC 0.932 (95% CI 0.894 to 969). Sensitivity 48.3%, specificity 96.9%. *Mechanical ventilation used as an indicator of smoke inhalation (patients with chemical injuries, scalds, and contact injuries were coded as "no mechanical ventilation" in the regression).

Table 5 – Linear simple regression for duration of hospital stay

	Coefficient	p	95% CI
O *(reference)*			
A	-11.49	0.11	-25.38 to 2.40
B	-6.58	0.49	-25.28 to 12.12
AB	-16.20	0.35	-50.61 to 18.21
Constant	51.77	0.000	41.47 to 62.08

Model $R^2 = 0.02$, p= 0.39, n=196 (survivors).

Table 6 – Linear multivariable regression for duration of hospital stay

	Coefficient	p	95% CI
Age, years	-0.02	0.74	-0.16 to 0.11
Superficial dermal BSA%	0.32	0.05	0.00 to 0.65
Deep dermal BSA%	0.35	0.03	0.04 to 0.67
Full thickness BSA%	1.00	<0.001	0.61 to 1.40
Mechanical ventilation*	-6.28	0.11	-14.05 to 1.49
Red blood cell transfusions	0.73	<0.001	0.52 to 0.93
Operations	2.40	0.002	0.88 to 3.92
Blood type:			
O *(reference)*			
A	-0.27	0.94	-7.11 to 6.57
B	0.25	0.96	-8.83 to 9.32
AB	4.85	0.57	-11.76 to 21.46
Constant	6.90	0.21	-3.84 to 17.63

Model adjusted $R^2 = 0.77$, $p < 0.001$, n=196 (survivors). *Mechanical ventilation used as an indicator of smoke inhalation (patients with chemical injuries, scalds, and contact injuries were coded as "no mechanical ventilation" in the regression).

Table 7 – Linear multivariable regression for days on mechanical ventilation

	Coefficient	p	95% CI
Age, years	0.10	0.04	0.01 to 0.19
Superficial dermal BSA%	0.29	0.008	0.08 to 0.51
Deep dermal BSA%	0.25	0.02	0.05 to 0.45
Full thickness BSA%	0.46	<0.001	0.22 to 0.70
Operations	2.41	<0.001	1.64 to 3.18
Blood type:			
O *(reference)*			
A	3.91	0.10	-0.70 to 8.51
B	-3.06	0.32	-9.15 to 3.03
AB	3.75	0.51	-7.45 to 14.94
Constant	-12.67	<0.001	-19.66 to -5.68

Model adjusted $R^2 = 0.51$, $p < 0.001$, n=196 (survivors), all days on mechanical ventilation are analysed in this regression. The variable Red blood cell transfusions was significant but it was removed as it disturbed (was correlated with) the variables burn size (all depths) and number of operations.

SUPPORTING INFORMATION

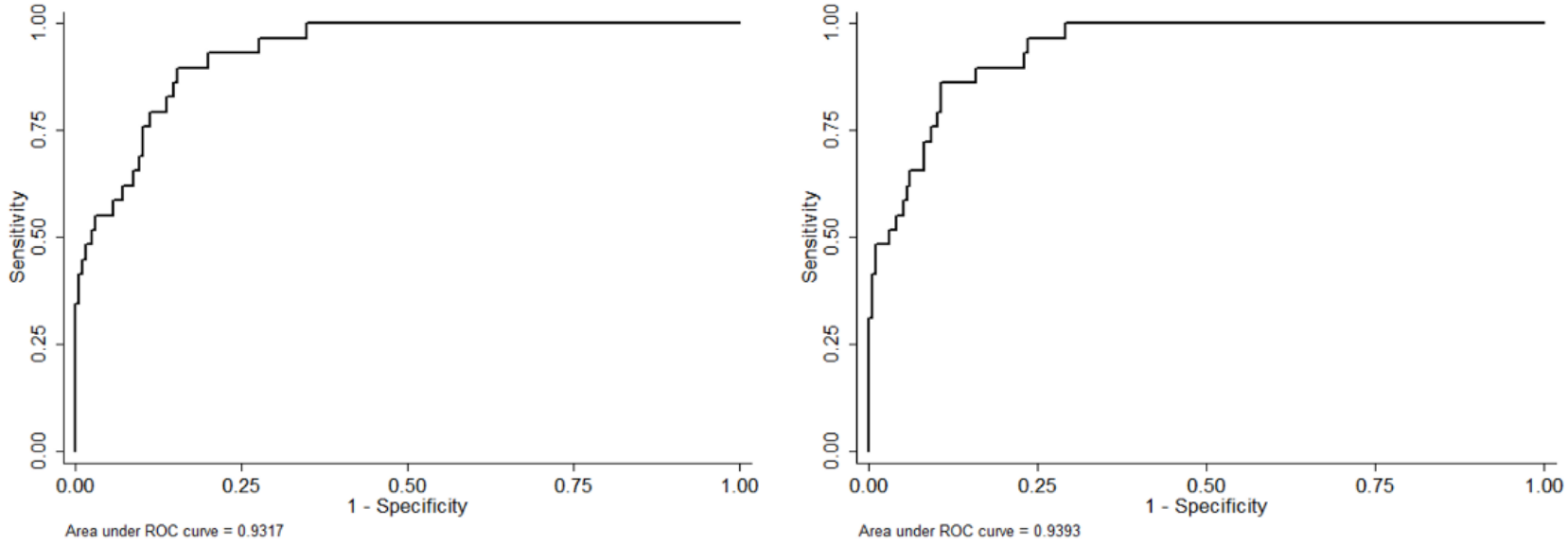

Figure 1. The left curve shows the ROC AUC of the regression model for mortality without blood type (AUC 0.932, 95% CI 0.894–0.970) and the right curve shows the same model but with the variable (categorical) blood type (AUC 0.939, 95% CI 0.905–0.974), chi squared p=0.24.