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Increased risk of blood transfusion in patients with diabetes mellitus sustaining non-major burn injury.

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ABSTRACT

Background: Due to the increased mortality and morbidity associated with blood transfusion, identifying modifiable predictors of transfusion are vital to prevent or minimise blood use. We hypothesised that burn patients with diabetes mellitus were more likely to be prescribed a transfusion. These patients tend to have increased age, number of comorbidities, infection risk and need for surgery which are all factors reported previously to be associated with blood use.

Objective: To determine whether patients with diabetes mellitus who have sustained a burn ≤20% total body surface area (TBSA) are at higher risk of receiving red blood cell transfusion compared to those without diabetes mellitus.

Method: This was a retrospective cohort study including patients admitted to the major Burns Unit in Western Australia for management of a burn injury. Only the first hospital admission between May 2008 to February 2017 were included.

Results: Among 2,101 patients with burn injuries ≤20% TBSA, 48 (2.3%) received packed red blood cells and 169 (8.0%) had diabetes. There were 13 (7.7%) diabetic patients that were transfused versus 35 (1.8%) non-diabetic patients. Patients with diabetes were 5.2 (p=0.034) times more likely to receive packed red blood cells after adjusting for percentage TBSA, haemoglobin at admission or prior to transfusion, number of surgeries, total comorbid burden and incidence of infection. As percentage TBSA increases, the probability of packed red blood cell transfusion increases at a higher rate in DM patients.

Conclusions: This study showed that diabetic patients with burn injuries ≤20% TBSA have a higher probability of receiving packed red blood cell transfusion compared to patients without diabetes. This effect was compounded in burns with higher percentage TBSA.

Keywords: Blood transfusion, Diabetes mellitus, Burns, Packed red blood cells, Blood use, Anaemia

1. INTRODUCTION

Anaemia is a pervasive complication in burn patients with injuries that involve as little as 10% total body surface area (TBSA).[1] To correct it, burn patients often require transfusion of blood products, particularly packed red blood cells (PRBC).[2-4] However, transfusions have been associated with increased mortality and infection in burn patients.[1, 5-8] As a result, the mechanisms responsible for anaemia post-burn and predictors of transfusion require exploration to develop patient risk profiles and means of reducing blood use.

The aetiology of anaemia after burn injury is multifactorial and can be broadly classified into acute blood loss and anaemia of critical illness.[3] Acute blood loss anaemia occurs within the first two weeks post-burn.[3] At most major burn centres, early tangential excision and grafting of burn wounds is standard practice as it reduces mortality and hospital length of stay (LOS).[9, 10] Unfortunately, significant haemorrhage often occurs as a consequence, leading to acute anaemia.[11] Conversely, anaemia of critical illness occurs between surgeries and throughout resolution of the injury.[12] The mechanisms underlying anaemia of critical illness are not fully established in the burn injury cohort; however, blunted erythropoiesis has been postulated as a major cause.[13-15] Other potential contributors include, iatrogenic blood loss,[16] nutritional deficiencies,[17] abnormal RBC morphology[18] and decreased RBC half-life through increased destruction[18] and sequestration.[19]

Several studies investigating determinants of anaemia after burn injury have found that %TBSA is the single most predictive independent variable.[2, 20, 21] Other reported predictors of blood transfusion include: increased age,[4, 5, 20] number of comorbidities,[22, 23] number of surgeries,[21] delayed time to primary excision,[20, 24] and wound infection.[20, 25] Many of these predictors coincide with risk factors and complications that are associated with diabetes mellitus (DM).

In Australia, an estimated 5.1% of the population have DM.[26, 27] Up to 70% of diabetics develop some degree of peripheral neuropathy; thus, predisposing them to burn injuries, especially on the lower extremities.[28-35] Diabetic patients are at risk of prolonged wound healing due to immune system impairment and peripheral vascular disease.[10, 29, 36-38]

Diabetics often have comorbid anaemia, even with normal renal function.[39, 40] This was demonstrated in an Australian cross-sectional survey which reported that 23% of diabetic patients were anaemic.[41] Although the aetiology of anaemia in DM is multifactorial, inappropriately low erythropoietin (EPO) is documented as a major cause.[42-44] Consequently, these factors may place DM patients at greater risk of requiring blood replacement.[45, 46]

Previous studies investigating the epidemiology and outcomes of DM in a burns setting have found a higher mortality rate and LOS amongst DM patients.[28, 30, 36, 47] DM burn patients are also reported to have increased: age,[28, 30, 48] number of comorbidities,[49, 50] infection risk,[36, 50, 51] need for surgery[30, 36] and time-to-wound-closure.[29] Furthermore, DM patients sustaining burns on the lower extremities often present after a delay.[36, 48, 49] Lower extremity burns themselves are also associated with increased incidence of infection, need for skin grafting and

LOS.[28, 30, 52] Based on these findings, it can be hypothesised that diabetic burn patients are at higher risk of being prescribed a transfusion.

There is only one study to date, conducted by Boral et. al.,[22] that investigates transfusion in burn patients with comorbidities and it was found that patients with DM had three times the odds of receiving blood products. Of the transfused group, there were more patients with comorbidities in the <20% TBSA group compared to the ≥20% TBSA group. Despite this, the association of specific comorbidities and risk of transfusion in patients <20%TBSA was not analysed.

To explore these results further, the current study aimed to determine whether ≤20% TBSA burn patients with DM were more likely to receive PRBC transfusion compared to non-diabetics (nDM). Although burns >20%TBSA has been associated with an increased risk of requiring blood transfusion,[5, 53-55] most burn injuries are ≤20%TBSA. Thus, this study was designed specifically to reduce this confounding factor. Burns with high %TBSA have a more complex recovery pathway with multiple factors such as multi-trauma and more frequent and extensive operations which increase the likelihood of transfusion.[1, 21, 56] Therefore, this study aimed to provide a more reliable evaluation of DM as an independent predictor for blood transfusion. Identifying an association between DM and the use of blood products may provide insight into how management can be targeted and expedited to reduce blood use and improve overall outcomes in burn patients with DM.

2. METHODS

2.1 Study design

This was a retrospective cohort study including patients admitted to Royal Perth Hospital and Fiona Stanley Hospital Burn Units in Western Australia for acute burn injury management. The project was approved by the Human Research Ethics Committees of the WA Department of Health (approval number 15-208).

2.2 Study protocol

This study utilised data from administrative and clinical databases populated by extracts from electronic medical records. Patients admitted to the single Western Australian Adult Burns Unit from May 2008 to October 2017 (inclusive) were eligible for inclusion. The subset of admitted burns patients who did not have a corresponding record in the linked Cube of Blood Related Activity (COBRA) database from May 2008 onwards were excluded as their transfusion status could not be determined. As we were interested in blood product use during the first hospital admission after a burn injury, admissions for reconstructive or further treatment were excluded.

Clinical information available for all first admissions after burn injury included %TBSA, body location, burn agent, type of surgery, length of hospital stay (LOS), number of units and type of blood products used, whether bleeding was recorded with transfusion and haemoglobin (Hb) levels. International Classification of Diseases (ICD) codes of inpatient records was used to identify patients with diabetes and additional comorbidity. Patients with intermediate glycaemia, type 1 DM, type 2 DM, other specified DM and unspecified DM were classified as DM for the purposes of this study. Additional comorbidities were identified as any of the 31 conditions of the Elixhauser comorbidity

index[57-59] in the current or past hospital admissions. The sum of Elixhauser conditions, representing the cumulative number of Elixhauser comorbidities (excluding diabetes) was used a measure of total comorbid burden. For analysis, Hb prior to transfusion was used if available; otherwise first Hb during admission was included. All data extracts provided to analysts were deidentified to ensure patient confidentiality.

2 .3 Statistical methods

Baseline patient and burn injury characteristics of the DM group and non-diabetic (nDM) group were described using descriptive univariate statistics. Equality of means were tested using independent t-tests and equality of proportions using Pearson's Chi-square tests. P values less than 0.05 were considered statistically significant. Multivariable logistic regression models were constructed to evaluate the association between DM and PRBC transfusion whilst accounting for other potential predictors of PRBC use, including Hb prior to transfusion or at admission. Variables were selected through a purposeful backward elimination in combination with clinical rationale. Plausible interaction terms between DM and other covariates were assessed using likelihood ratio tests. The optimal functional form of continuous variables age and %TBSA were identified. Tests for model misspecification and goodness of fit and assessment of influential observations were performed. Statistical analyses were conducted using Stata version 15.

3.   RESULTS

A total of 2,211 patients had a first admission for a burn injury and had a match in the COBRA database. Of these patients, 111 (5.0%) burns patients received a blood transfusion. After excluding patients with >20% TBSA, there remained a total of 2,101 patients, of whom 169 (8.0%) had DM (Fig 1).

3.1 Patient demographics and burn characteristics

Burns patients with DM were significantly older and had more comorbidities. DM patients also had a longer average hospital LOS of 4.2 days. Burns incurred by diabetics were more likely to be smaller, full-thickness, on the feet and due to scald and contact injuries. DM patients underwent more surgeries and were more likely to have post-trauma and/or post-surgical wound infection. There were no differences in type of surgery required.

3.2 Blood use

Hb was categorised into <80, 80-90 and >90. More patients with DM had a lower haemoglobin at admission or prior to transfusion compared to patients without DM (Table 2). Although it appears there are relatively less nDM patients who had Hb >90g/L, this is due to more nDM patients not having a Hb measured throughout admission. As it is a requirement that Hb is measured when receiving a transfusion, it can be assumed that patients without a Hb recorded were not transfused.

A significantly higher proportion of patients with DM patients received blood products (7.7%) compared to patients without DM (1.8%) (p<0.001). Most of these transfusions were PRBCs. There was no difference in FFP or platelet transfusions. No patients received cryoprecipitate and are

therefore not represented in the table. The number of total units of PRBC received was also found not to be significantly different between DM and nDM patients overall and with/without bleeding recorded with transfusion.

3.1 Factors associated with packed red blood cell transfusion

Multivariable logistic regression models were constructed to determine whether the observed univariate association of DM with increased PRBC use remains after controlling for other factors, including Hb prior to transfusion or at admission. Patients with DM were 5.2 (95%CI 1.1-24.0) times more likely to receive PRBC after averaging over TBSA, Hb level, total comorbid burden, number of surgeries, and incidence of wound infection (Table 3). On average every increase of 1% TBSA was associated with a 40% increased odds of PRBC use. Age, burn depth and burn site were not associated with the odds of a blood transfusion in the regression models.

However, a significant interaction between %TBSA and DM was observed, indicating that the odds of a PRBC transfusion with increasing %TBSA was greater in patients with DM compared to patients without DM (Table 3). The predicted probability of receiving PRBC by diabetic status for increasing %TBSA is represented in Figure 2. This shows that the difference in transfusion probability between DM and nDM groups becomes significant from 15% TBSA onwards. At 20% TBSA DM patients have a 98% (95%CI: 90-105%) probability of a PRBC transfusion compared to a 18% (95%CI: 5-31%) probability for nDM patients of the same %TBSA.

4. DISCUSSION

The study showed that in Western Australia, adult diabetic burns patients with injuries ≤20% TBSA had a five-fold increase in the odds of PRBC transfusion during the first burn admission compared to patients without DM after accounting for important predictors of blood transfusion. This builds on the findings from Boral et al.[22] who also reported increased odds of transfusion among DM patients. In contrast to that study, our odds ratio is higher which may be due to our analysis being restricted to burns ≤20%TBSA and we have adjusted for %TBSA, baseline Hb level, surgery and infection in our logistic model. The current study has also found that as %TBSA increases, the probability of PRBC transfusion increases at a higher rate in DM patients. This indicates that the effect of DM on odds of transfusion is greater in burns with increasing %TBSA.

We observed that patients with DM had a lower Hb at admission or prior to transfusion compared to patients without DM. This concurs with the previously documented association between anaemia and DM.[39, 41] Despite this, DM remained significantly associated with PRBC transfusion even though Hb levels were accounted for in the multivariable regression model. It is worth noting that anaemia secondary to nutritional deficiencies and/or blood loss were also included in the sum of Elixhauser conditions and were thus accounted for in the analysis. This indicates that PRBC transfusion in burn patients with DM is not solely explained by Hb level or comorbid anaemia but is the result of unknown and/or unmeasured driver(s) that may be related to DM pathology.

Increasing %TBSA, number of surgeries, number of comorbidities and incidence of wound infection were also confirmed to be independently associated with increased odds of PRBC transfusion in this

study. All are well established predictors PRBC transfusion, with %TBSA reported as the most predictive burn-related variable.[2, 20, 21, 25, 30, 36] Previous studies have also reported that increased age[4, 5, 20] is associated with increased risk transfusion in burn patients. However, we found this association to be non-significant after adjusting for sum of comorbidities which is strongly age-related.

There was a 0.8-unit difference in the mean of cumulative PRBC required between DM and nDM patients; however, this did not reach statistical significance. This result was not surprising in a cohort with non-major burn injuries. However, it coincides with findings from Boral et al.[22] who did not restrict %TBSA yet also report that units of PRBC transfused was similar in burn patients with or without comorbidities. It is also apparent that there was a 0.9-unit non-significant difference in units of PRBC transfused for bleeding/blood loss in DM versus nDM patients. This insinuates that DM patients may require more replacement for blood loss; however, this finding needs to be confirmed in a larger study with more statistical power.

Here we report that five percent of all burn patients admitted to the only dedicated adult burns unit in Western Australia received a blood transfusion. Among patients with burns ≥20%TBSA, approximately half received blood products. These values are much less than those reported in other settings. Koljonen et al. [4] found 34% of all burn patients treated at a major Finnish burn centre received a blood transfusion. However, this study did not determine mean or median burn %TBSA and thus direct comparison is difficult. Similarly, in regional burn centres throughout the United States and Canada, Palmieri et al. [5] reported that 74.7% of burn patients with ≥20%TBSA received blood products. These differences may be partly explained by differences in patient samples; however, it also suggests there is variation in burn management and/or transfusion practices over time and hospital location. In the 2008-2009 financial year, Western Australia had one of the lowest PRBC issuance rates in the developed world.[60] Since then, this rate has decreased further by approximately 40% due to the implementation of the Patient Blood Management (PBM) program.[61] PBM strategies are well documented to reduce blood use[62-64] and Western Australia was one of the first places worldwide to implement a health-system-wide PBM program.[61] The WA burns service has driven a focused surgical plan aimed at limiting perioperative blood loss with the goal of reducing the need for PRBC specifically in the non-major burn injuries. Hence, differences in transfusion practice linked with surgical practise may be the major driver of the lower transfusion rates found in this study.

There were several limitations in this study. Firstly, the small number of DM patients and low incidence of transfusions in patients ≤20% TBSA mean that our study only had sufficient statistical power to detect large effect sizes. A larger cohort of diabetic patients would allow refinement of the effect size with greater precision. Fortunately, as the final model showed evidence that TBSA modified the association of diabetes with PRBC transfusion with a p-value of <0.001, the probability of a Type 1 error is very small. A small cohort also meant that performance of mediation analysis was impractical. As this study found that DM is an independent risk factor for PRBC transfusion, it would have been interesting to further explore this relationship, such as determining whether Hb has a mediator role. Secondly, this study did not have access to blood glucose level (BGL) and glycated haemoglobin concentration (HbA1c). BGL and HbA1c could enable identification of previously undiagnosed DM and patients who developed glucose intolerance, insulin resistance or

DM due to their burn. Burn injuries can cause profound hypermetabolism and stress responses resulting in hyperglycaemia and newly diagnosed DM.[65] Thirdly, this study was unable to account for variables such as reason for transfusion (other than Hb level), use of anticoagulants, and preferences of the clinician (including attending surgeon and anaesthetists) as these were not recorded. However, variation between clinicians at Fiona Stanley Hospital is likely to be minor due to the implementation of a hospital-wide transfusion protocol with strict evidence-based transfusion thresholds for specific clinical situations. This facilitates standardisation of transfusion practices and hence, deviance from this due to clinician preference would be minimal. Furthermore, the restriction of this study to a single Burns centre in Australia further limits the potential variability between clinicians. Nevertheless, these factors have been reported to be associated with blood loss and/or transfusion in previous studies.[5, 20, 24, 25, 54, 55] Hence, not accounting for these introduces potential confounding. Lastly, this study relied on administrative data collected for non-research purposes which subsequently lacked clinical detail; and a manual chart review that has several potential sources of measurement error.

Despite these limitations, the cohort is likely to be an accurate representation of the study population in Western Australia. The 8% of DM in this sample was deemed appropriate as the prevalence of DM in Western Australia is estimated to be 6.3%[66] and it was predicted that diabetics are at an increased risk of burn injury.[29, 30] Furthermore, all patients who received a transfusion and had a burn ≤20% TBSA were included. Hence, the positive results of this study provide justification for future studies to be conducted to elucidate the relationship between DM and blood transfusion. As this study accounted for Hb levels and anaemia, further research including prospective studies are required to explore the reason(s) and mechanism(s) behind increased transfusion in DM burn patients. For instance, although burn %TBSA is a marker of burn severity, the actual mechanism underlying the effect of %TBSA, on increased probability of transfusion in diabetics needs to be investigated. Inclusion of BGLs and HbA1c, surgeon preference or rationale, details of medication use would also be beneficial in future studies. HbA1c may be of particular benefit to determine the relationship between DM control or severity and blood use.

4.1 Potential clinical application

The finding that a higher proportion of diabetic burn patients receive blood compared to non-diabetics has potential clinical application. Identification of DM as a risk factor may enable more accurate prediction of blood requirements and thus, more appropriate use of blood products. Furthermore, transfusions may be pre-empted and prevented by addressing the patient's risk factors and performing timely investigations to optimise their physical condition before a transfusion is considered.[67-69] This is the core principle of the PBM program which has significantly reduced mortality and morbidity due to transfusion in Western Australia.[61]

As DM patients are more likely to have iron deficiency anaemia due to dysregulation of iron homeostasis,[70, 71] administering intravenous (IV) iron may reduce the need for blood transfusion. There is a consensus in the literature which supports the safety and efficacy of pre-operative IV iron in patients who have iron deficiency anaemia and surgery is needed within 6 weeks.[72] Furthermore, there is evidence that IV iron is effective in increasing Hb levels in DM due to decreased intestinal iron absorption.[73] Similarly, it may be clinically appropriate to administer

recombinant human erythropoietin (EPO) to DM patients. The inability to produce EPO in response to a reduction of Hb is a major cause of anaemia in diabetics.[42-44] This is most pronounced in patients with renal impairment; however, 70% of anaemic patients without renal impairment are also prone to inappropriately low EPO levels.[43] Several randomised controlled trials have shown reduced transfusion rates with a short pre-operative regimen of EPO[74] or a single dose of EPO plus IV iron in the pre-operative[75] or intra-operative period.[76] In addition, there is accumulating evidence for the use of EPO as a neuroprotective agent to modulate neuroinflammation and prevent apoptosis in burns injuries.[77] DM patients may derive benefit from this additional effect of EPO due to the pro-inflammatory nature of DM[78] and its association with neuropathic complications.[79, 80] Therefore, there is rationale to conduct prospective trials to evaluate the efficacy of EPO in diabetic burn patients in the future.

5. CONCLUSION

Diabetic patients with burn injuries ≤20% TBSA have a higher probability of receiving PRBC transfusions compared to patients without diabetes. Increased odds of PRBC transfusion were also found with known risk factors at admission including increasing %TBSA, low baseline Hb, and number of comorbidities. Increased odds of transfusion were also associated with surgery and development of infection. Overall, transfusion rates in Western Australia are relatively low compared to other developed countries and may be attributed to the health-system wide Patient Blood Management Program.

DECLARATION OF INTEREST
Declarations of interest: none

FIGURE CAPTIONS
Figure 1. Patient selection flow diagram.

(red colour in picture)

Figure 2. The association of percentage total body surface area (%TBSA) with probability of packed red blood cell (PRBC) transfusion in patients with and without diabetes mellitus.

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Table 1. Patient, burn characteristics and hospital outcomes of diabetic (DM) and non-diabetic (nDM) burn patients.

	nDM (n=1932; 92.0%)		DM (n=169; 8.0%)		p-value
Mean age at admission (SD)	36.8	16.4	58.4	15.5	<0.001
Male sex, n (%)	1394	72.2	119	70.4	0.629
Mean sum of Elixhauser conditions (SD)	0.5	1.1	2.4	2.5	<0.001
BURN CHARACTERISTICS					
% TBSA					
Mean (SD)	4.1	4.3	3.4	3.8	0.036
Median (IQR)	2.5	1-5	2	1-4.5	0.027
Burn site, n (%)					
Head and/or neck	554	28.7	29	17.2	0.001
Torso	434	22.5	36	21.3	0.728
Arm(s)	675	34.9	33	19.5	<0.001
Hand(s)	551	28.5	26	15.4	<0.001
Genitals and/or buttocks	121	6.3	12	7.1	0.668
Leg(s)	805	41.7	60	35.5	0.118
Foot/feet	261	13.5	57	33.7	<0.001
Respiratory/internal	33	1.7	7	4.1	0.026
Maximum burn depth					
Superficial	103	5.3	1	0.6	0.001
Partial thickness	1449	75.0	119	70.4	
Full thickness	380	19.7	49	29.0	
Principal burn mechanism, n (%)*					
Flame	956	49.5	57	33.7	<0.001
Scald	520	26.9	60	35.5	
Contact	245	12.7	38	22.5	
Chemical	125	6.5	8	4.7	
Radiation	13	0.7	6	3.6	
ADMISSION CHARACTERISTICS					
Mean length of stay (SD)	6.1	6.4	10.3	10.0	<0.001
ICU admission, n (%)	54	2.8	9	5.3	0.064
Wound infection (n, %)	176	9.1	31	18.3	<0.001
Surgery (n, %)#	1237	64.0	103	61.0	0.424
Non-excisional debridement	89	4.6	13	7.7	0.073
Excisional debridement	173	9.0	11	6.5	0.281
Split skin graft	1156	59.8	93	55.0	0.222
Recell	661	34.2	43	24.4	0.021
Mean number of surgeries (SD)	1.1	0.42	1.2	0.86	0.006

SD, standard deviation; IQR, interquartile range; ICU, intensive care unit

*Excluded friction and electrical burns as no DM patients incurred these injuries

#Excluded escharotomy/depression fasciotomy, synthetic skin graft and full thickness skin graft due to low numbers and no DM patients had these procedures.

Table 2. Comparison of blood use between patients with and without diabetes mellitus					
	nDM (n=1932; 92.0%)		DM (n=169; 8.0%)		p-value
Baseline Haemoglobin (n, %)					
<80 g/L	18	0.9	6	3.6	
80-90 g/L	4	0.2	6	3.6	<0.001
>90 g/L	1240	64.2	137	81.1	
Blood product (n, %) *					
Any blood products	35	1.8	13	7.7	<0.001
PRBC	33	1.7	13	7.7	<0.001
FFP	3	0.2	1	0.6	0.212
Platelets	2	0.1	0	0	0.676
Mean units of PRBC received (SD)					
Overall	2.8	2.4	3.6	3.0	0.309
Bleeding recorded with transfusion	4.6	3.6	5.5	3.4	0.631
Bleeding not recorded	2.0	1.0	2.0	1.0	0.927

SD, standard deviation; PRBC, packed red blood cells; FFP, fresh frozen plasma
*No patients received cryoprecipitate

Table 3. Factors associated with odds of transfusion of packed red blood cells during first admission following burn injury.			
Factors	**OR**	**95%CI**	**p-value**
Diabetes mellitus (main effect only)	5.2	1.1-24.0	0.034
% TBSA (main effect only)	1.4	1.3-1.6	<0.001
As 2-way interaction*			
No DM			
%TBSA	1.4	1.2-1.5	<0.001
With DM			
%TBSA	2.0	1.5-2.7	<0.001
Other factors			
Hb (g/L)			
>90	1.0	Ref	-
80-90	85.1	8.8-818.2	<0.001
<80	1613.8	94.5-27554.7	<0.001
Sum Elixhauser conditions (excl.DM)	2.7	1.5-4.6	<0.001
Number of surgeries	2.0	1.1-3.8	0.029
Wound infection	3.7	1.0-13.2	0.048

*OR from a 2-way interaction term between diabetes and %TBSA. For both non-diabetics and diabetics, the probability of being transfused with PRBC varied with %TBSA and is visualised in Figure 2.
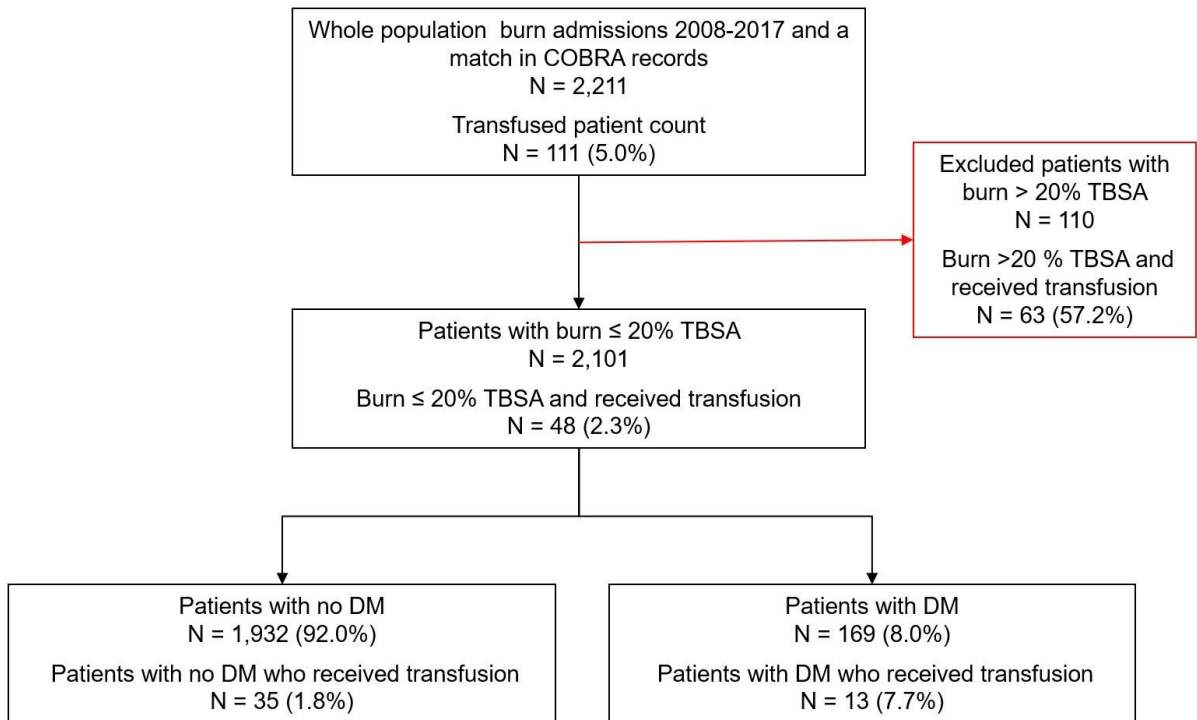
Figure 1

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┌─────────────────────────────────────────┐
│  Whole population  burn admissions       │
│  2008-2017 and a match in COBRA records  │
│              N = 2,211                    │
│                                           │
│       Transfused patient count            │
│          N = 111 (5.0%)                   │
└─────────────────────────────────────────┘
                    │
                    │          ┌─────────────────────────────┐
                    │────────▶ │  Excluded patients with      │
                    │          │  burn > 20% TBSA             │
                    │          │       N = 110                │
                    │          │                              │
                    │          │  Burn >20 % TBSA and         │
                    │          │  received transfusion        │
                    │          │     N = 63 (57.2%)           │
                    │          └─────────────────────────────┘
                    ▼
┌─────────────────────────────────────────┐
│     Patients with burn ≤ 20% TBSA        │
│              N = 2,101                    │
│                                           │
│  Burn ≤ 20% TBSA and received transfusion │
│          N = 48 (2.3%)                    │
└─────────────────────────────────────────┘
          │                        │
          ▼                        ▼
┌──────────────────────┐  ┌──────────────────────┐
│  Patients with no DM  │  │   Patients with DM    │
│   N = 1,932 (92.0%)   │  │    N = 169 (8.0%)     │
│                       │  │                       │
│ Patients with no DM   │  │ Patients with DM who  │
│ who received          │  │ received transfusion  │
│ transfusion           │  │   N = 13 (7.7%)       │
│   N = 35 (1.8%)       │  │                       │
└──────────────────────┘  └──────────────────────┘
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Figure 2