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Short Communication

A standards-based application for improving platelet transfusion workflow

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ABSTRACT

Objective: Thrombocytopenia is a common complication of hematopoietic stem-cell transplantation (HSCT), though many patients will become immune refractory to platelet transfusions over time. We built and evaluated an electronic health record (EHR)-integrated, standards-based application that enables blood-bank clinicians to match platelet inventory with patients using data previously not available at the point-of-care, like human leukocyte antigen (HLA) data for donors and recipients.

Materials and methods: The web-based application launches as an EHR-embedded application or as a standalone application. The application coalesces disparate data streams into a unified view, including platelet count, HLA data, demographics, and real-time inventory. We looked at application usage over time and developed a multivariable logistic regression model to compute odds ratios that a patient undergoing HSCT would have a complicated thrombocytopenia course, with several model covariates including pre-/post-application deployment.

Results: Usage of the application has been consistent since launch, with a slight dip during the first COVID wave. Our model, which included 376 patients in the final analysis, did not demonstrate a significantly decreased odds that a patient would have a complicated thrombocytopenia course after application deployment as compared to before application deployment.

Discussion: We built an EHR-integrated application to improve platelet transfusion processes. Whereas our model did not demonstrate decreased odds of a patient having a complicated thrombocytopenia course, there are other workflow and clinical benefits that will benefit from future evaluation.

Conclusion: A web-based, EHR-integrated application was built and integrated into our EHR system and is now part of the standard operating procedures of our blood bank.

Background

Thrombocytopenia is a common complication of hematopoietic stem-cell transplantation (HSCT), and many patients require platelet transfusion support while undergoing treatment. In the USA, approximately 2.2 million platelet doses are transfused annually, most of which are done prophylactically in the setting of HSCT or chemotherapy to reduce the risk of life-threatening bleeding.[1,2] Because platelet units are stored at room temperature their shelf life is only 5–7 days, platelet inventory management and optimal platelet use are particularly important for ensuring availability.[3]

Platelet transfusion refractoriness (PTR), in which a patient fails to respond to platelet transfusions, is a common clinical problem for patients undergoing HSCT.[4] PTR is broadly classified into immune and non-immune causes. Non-immune causes, such as infection, disseminated intravascular coagulation, endothelial injury syndromes, splenomegaly, or medications,

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are more common.[5] Immune causes, notably alloimmunization to human leukocyte antigen (HLA), human platelet antigens, and/or ABO antibodies, frequently impact HSCT patients given significant previous transfusion alloimmunization exposures and post-transplantation platelet transfusion dependency before engrafted stem cells start making a sufficient number of platelets.[6]

One strategy to address PTR in alloimmunized patients is to avoid donors against which the patient has pre-existing anti-HLA Class 1 antibodies, and secondarily to seek platelet donors that have minimal HLA Class 1 mismatch with the patient. It is estimated that up to 25% of patients requiring multiple platelet transfusions require HLA matching.[7] However, because HLA-matched platelets are more expensive, difficult to obtain, and require more time to prepare,[4] matching is often not used until a patient has repeatedly demonstrated PTR. As such, previously, we only provided HLA-matched platelets for a small number of patients identified by clinicians as not responding to platelet transfusions, followed by HLA testing to identify anti-HLA antibodies with a calculated panel reactive antibody (cPRA) $\geq 80\%$. Additionally, most institutions employ a "first in, first out" approach to platelet transfusion given the limited shelf life of platelets. However, nearly all HSCT recipients undergoing allogeneic transplantation have already had HLA antibody testing performed as part of their transplant evaluation. Therefore, if local platelet donors are also HLA typed, it should be possible to avoid anti-donor HLA class 1 antibody and minimize donor HLA mismatch using HLA matching or HLA antigen avoidance for a more targeted approach in which specific platelet units from inventory are selected for each patient. Historically, even if such information was available, this personalized selection process for all patients with ancillary transplant-based HLA data was never considered at our institution because HLA platelet compatibility evaluation and product selection was a time-consuming manual process. Traditionally, it typically involved determination of the cPRA score which is a percentage of the population to which detected alloantibodies would bind,[8] determination of a match "grade" for each platelet and recipient based on the number of match antigens, and evaluation for cross-reactivity of patient alloantibodies and donor antigens,[5] sometimes referred to as a "virtual crossmatch." However, if these steps could be performed algorithmically by software, it would enable blood bank personnel to efficiently employ this more personalized platelet transfusion approach at the point of care.

To bring these different data points together in real-time, we built an electronic health record (EHR)-integrated, standards-based health information technology (IT) application for use by blood bank personnel. Our hypothesis was that bringing together multiple data streams for use in real-time by blood bank personnel could greatly improve platelet transfusion management. We describe the application here as well as usage metrics. We also look at clinical outcomes associated with usage of the app—specifically the number of platelet transfusions required and number of patient-days below a platelet count of 10,000 across different populations.

Methods

Application description

The application is shown in Fig. 1. It is a web-based app, built using the Angular[9] front-end web development platform, with a backend using igia,[10] a healthcare-focused open-source technology development platform created by our team. The application can launch as an embedded application within our EHR (Epic Systems, Verona, WI), or as a standalone application via a modified SMART on Fast Healthcare Interoperability Resources (FHIR) approach.[11] If the application is launched from within the EHR, patient context information (e.g., name, MRN) is passed to the application automatically. Otherwise, the patient must be manually selected.

The application includes five main components or "cards", detailed in Table 1. The first card is the Patient Card, and includes basic demographic data about the patient, along with their ABO RH type, last platelet count, and a platelet transfusion threshold, which can be set within the card. The second card is the cPRA card, and includes the HLA data about the patient, including their HLA type, alleles, HLA antibodies, and corresponding unacceptable platelet antigens. The FHIR interface that enables this card has been previously described.[12] Additionally, the cPRA card includes a real-time calculated cPRA score. cPRA is a score derived from comparing recipient HLA data to a national population frequency of unacceptable HLA antigens and results in a score from 0% to 100%. The cPRA calculator is a separate, open-source application, and has also been previously described.[13] The Blood Bank Inventory card is a real-time view into our institution's platelet inventory. The Inventory card includes a sorting algorithm that ranks available platelet supply based on match grade and antibody avoidance (described below). The Platelet Count & Procedures card graphically displays the patient's platelet count over time, with certain events overlaid, including the day 0 of their transplant (if applicable), and any prior platelet transfusions they received. Finally, the Whiteboard card allows blood bank clinicians to leave patient-specific notes.

There are several data integrations required to support the application, also highlighted in Table 1, many of which leverage existing FHIR interfaces available at our institution. Others were custom built to support this application, like the HLA FHIR interface, described previously.[12]

Platelet transfusion selection and workflow

Fig. 2 demonstrates the platelet transfusion workflow. In the standard operating procedures (SOPs) formulated in conjunction with the application going live, only patients undergoing HSCT would be viewed in the app, and only receive the best match platelet unit if their cPRA score was greater than 20%. All other patients would be identified as before by clinician request for matched platelets that triggers a transfusion medicine consult and HLA testing, but after this testing product selection could now be managed through the app. Patients with cPRA $\geq 80\%$ were put on formal HLA match restrictions in our blood bank system, so that units would be ordered from a regional blood supplier if our local platelet unit inventory did not have a compatible unit. Available platelet units in the donor system are classified based on match quality. An "A" match means 4/4 donor antigens are identical to the recipient; an "X" match means there are cross-reactive antigens present. Available units are then sorted, with "A" matches on top, and all "X" matches on the bottom.

Analysis

We looked at application usage over time by examining unique blood bank personnel as well as unique patients loaded into the application. To examine the clinical impact of the application, we grouped patients into three buckets: a "pre" group, which included patients undergoing HSCT before the application launched, a "washout" group, which included patients undergoing HSCT in the first 3 months after the application launched (to account for training and workflow changes), and a "post" group, which included everyone else. We included patients undergoing allogeneic HSCT from October 1, 2016, through September 1, 2022, with a diagnosis of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), non-Hodgkin lymphoma (NHL), and myelodysplastic syndrome (MDS) who required at least one platelet transfusion.

Statistical analysis

We calculated the median number of platelet transfusions required within 30 days of transplant, segmented by underlying diagnosis (AML, ALL, NHL, MDS/MPN) and induction chemotherapy intensity (myeloablative or reduced intensity chemotherapy) for eligible patients before the application launched and after launch (and after the 3-month washout period). We then calculated the median 30-day platelet count for the same population. We performed a multivariable logistic regression to compute odds ratios (ORs) with 95% CIs for the odds that a patient undergoing HSCT would have a complicated thrombocytopenia course, defined as requiring more than four platelet transfusions or having a 30-day median platelet count of less than 20,000 platelets per microliter (μL). Model

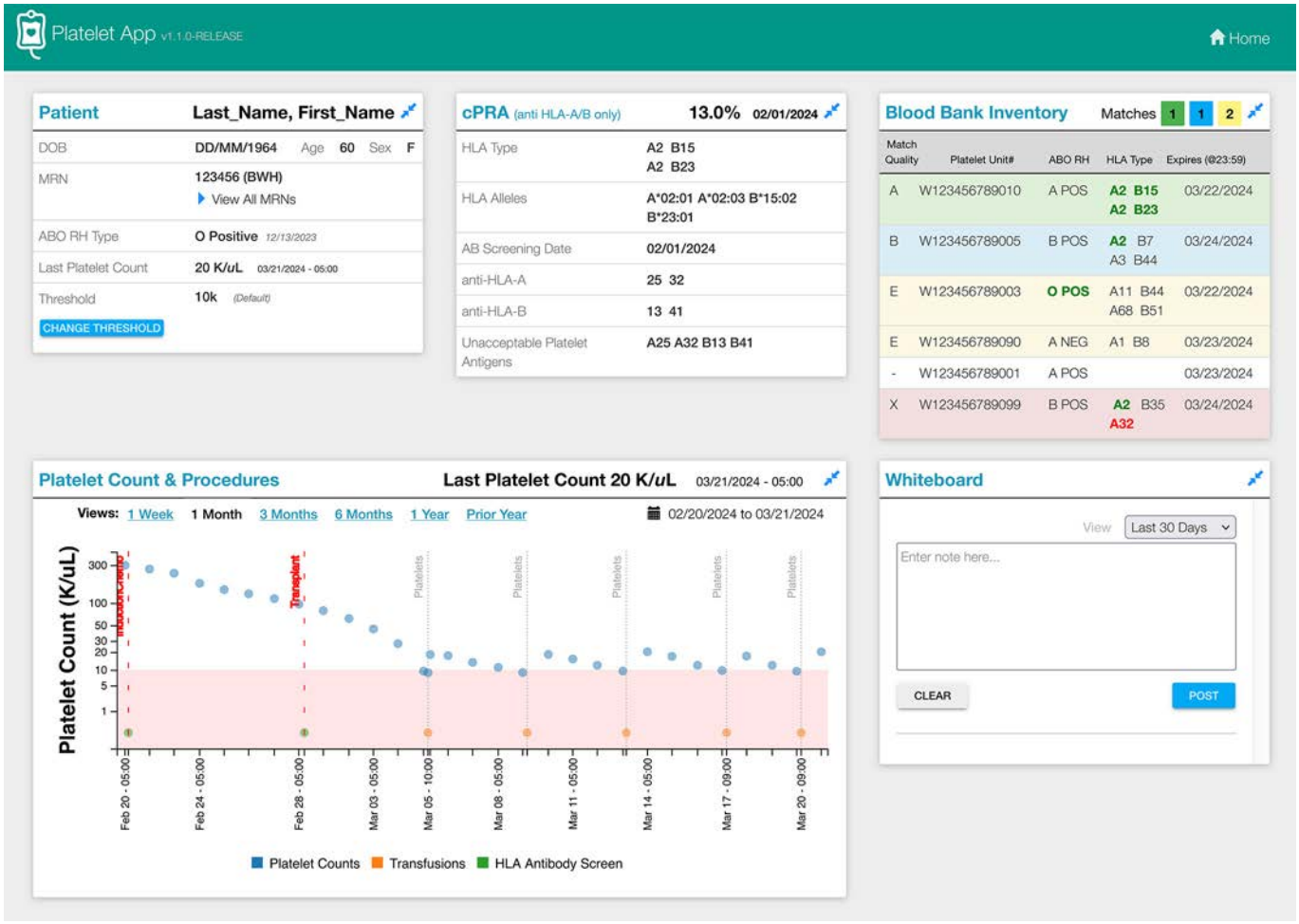

Fig. 1. The platelet application. The application includes five "cards" – the Patient card, the cPRA card, the Blood Bank Inventory card, the Platelet Count & Procedures card, and a Whiteboard card, each with distinct data and functionality.

Table 1
The Platelet App. The app consists of five "cards" that provide different functional components.

Application card	Data presented	Data integration	Highlighted functionality
Patient	• Patient demographics (name, DOB, gender, medical record number) • ABO RH type • Last platelet count • Transfusion threshold	• Custom EHR interfaces demographic • FHIR R2	Per guidelines, the default transfusion threshold is a platelet count of 10,000; this can be adjusted in this card as appropriate
cPRA	• HLA-A/B cPRA score • HLA type • HLA alleles • Antibody screening date • HLA-A and HLA-B antibodies • Unacceptable platelet antigens	• HLA as a FHIR interface from tissue type	cPRA score is calculated in real-time using an open-source web service developed for this application
Blood Bank Inventory	• Each platelet unit in our blood bank • Match quality • ABO RH • HLA type • Expiration date • Unit status (IN = available, XM = cross-matched)	• Custom interfaces to blood bank database	Platelet units are sorted and colored by match quality, where "A" is green with 4/4 HLA match; "B" is blue with a at least 1 HLA match and others avoiding alloantibodies; "E" is yellow with complete mismatch, but still all avoid alloantibodies; "-"is white with no HLA typing of donor; and "X" is red with an unacceptable antigen in the donor unit that would react with an alloantibody in the recipient.
Platelet Count & Procedures	• Platelet count by date • Stem-cell transplant date • Platelet transfusions, by date	• Platelet count is EHR FHIR interface • Transfusions are non-FHIR EHR interface	Timeseries X axis can be adjusted for closer or expanded views of the patient's clinical history
Whiteboard	• Whiteboard note	• None	Whiteboard is patient-specific, but persists across multiple users, allowing clinicians to leave notes about a patient

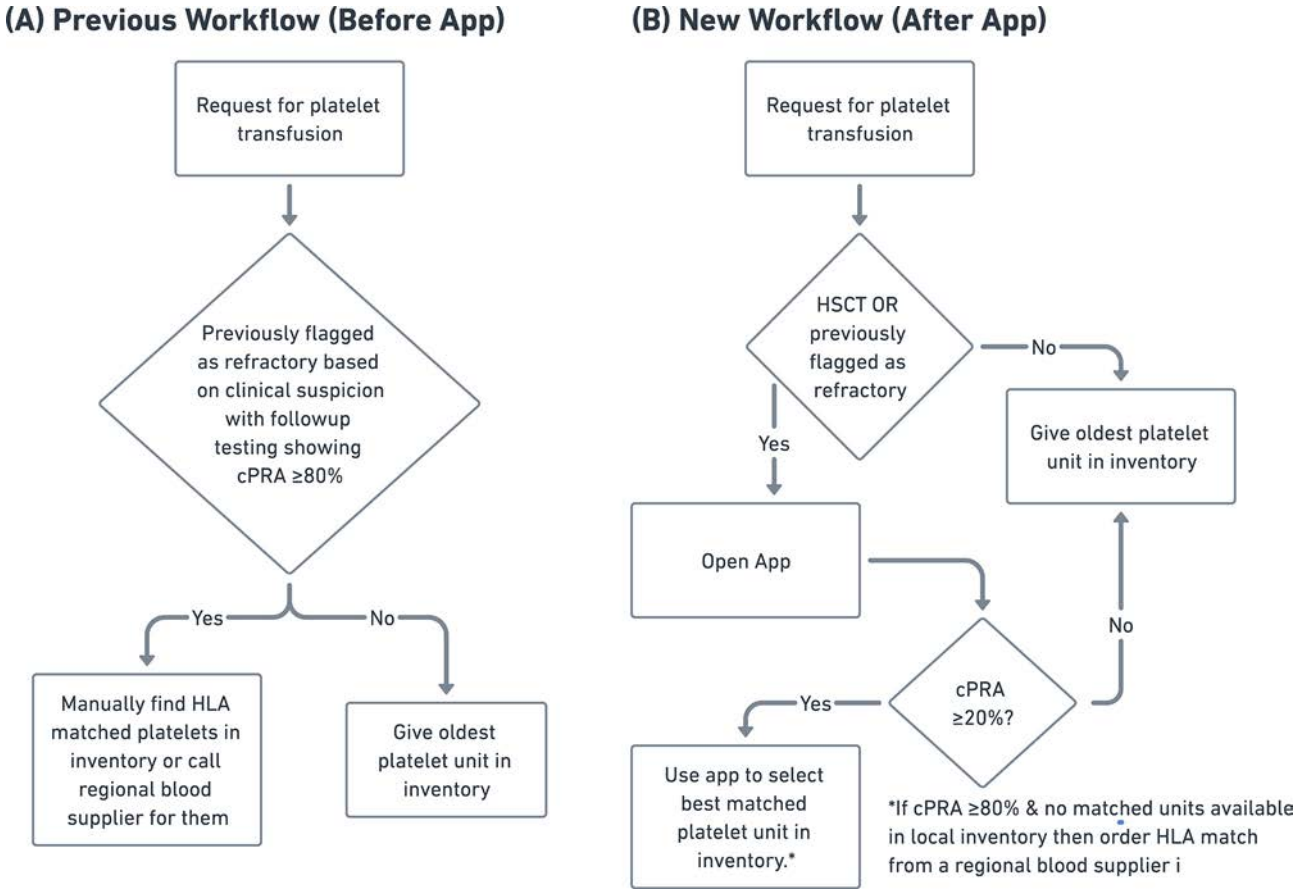

Fig. 2. Platelet transfusion workflows. Our standard operating procedures of cPRA ≥ 80% were expanded after the application launch to also include all allo-HSCT patients with a cPRA ≥ 20%.

covariates included pre/post "app" implementation (October 1, 2018), underlying HSCT diagnosis (ALL, MDS/MPN, NHL, AML), induction chemotherapy intensity (reduced intensity or myeloablative), and HLA transplant match category ("high" defined as 9 or 10 out of 10 allele-matched donor, "low" as <9).

Data analysis was conducted using R statistical software, version 3.5.1 (R Project for Statistical Computing). The Institutional Review Boards at Mass General Brigham and the Dana Farber Cancer Institute both approved this study.

Results

Development of the application started in 2016 and was completed in 2018. After several months of testing and modifications to the blood bank SOPs, the application went into production October 1, 2018. Before going live, a multi-disciplinary team met and conducted a hazard analysis for the application, listing potential unanticipated adverse events or failures, along with likelihoods as well as mitigations, to ensure appropriate remediations were in place. Autologous transplant patients were excluded because they usually do not have previously performed HLA testing. Other exclusions included patients with a transplant-date cPRA <20%, and infrequently transplanted diseases. Our final study population included 376 patients—132 in the "pre" group (transplanted before application launch on October 1, 2018), 15 in the "washout" group (transplanted from October 1, 2018 through January 1, 2019), and 229 in the "post" group, transplanted from January 1, 2019 through September 1, 2022 (Fig. 2).

Fig. 3 shows application usage by month since application go-live, with two trend lines: unique users (e.g., blood bank clinicians/technologists) and unique patients (how many different patients were loaded into the application that month). Usage patterns show consistent and steady usage of the application from onset, with expected decline in usage especially around our initial COVID surge. (See Fig. 4.)

In a multivariable model, we found that usage of the application did not significantly decrease the odds that a patient would have a complicated thrombocytopenia course, though there was a trend towards improvement (adjusted OR, 0.86; 95% CI, 0.54–1.36; $P = 0.518$). HSCT patients with an underlying diagnosis of MDS or MPN, as well as patients with a low HSCT match quality (<9/10), were more likely to have a complicated thrombocytopenia course (adjusted OR, 3.26; 95% CI, 1.09–11.06; $P = 0.0412$; and adjusted OR, 2.17; 95% CI, 1.2–3.96; $P = 0.0106$, respectively) (Table 2).

Discussion

We built a point-of-care, standards-based, health IT application to improve platelet transfusion processes at our institution. Our application brings multiple different data streams into one view and enables new mechanisms of assigning platelets for HSCT patients. The application is now part of the SOPs of our blood bank. Our initial results show a trend, though not statistically significant, towards improved clinical outcomes for the current subset of patients for which the application is being used.

Others have created generalized algorithms for HLA matching in the past,[14] including a publication on use of software for finding HLA-matched platelets for 10 patients with platelet refractoriness over a 10-day period.[15] However, a key innovation of our application is the aggregation and unified display of data that were previously available but difficult to collect and synthesize at the point of care, including HLA data alongside previous platelet transfusion history and platelet counts. In addition, in this study we present usage data for nearly 6-year period with over 1500 patients. Transplant recipient HLA data, for example, is generated by our typing lab, but usually only available as a Portal Document Format file in our EHR. Similarly, cPRA

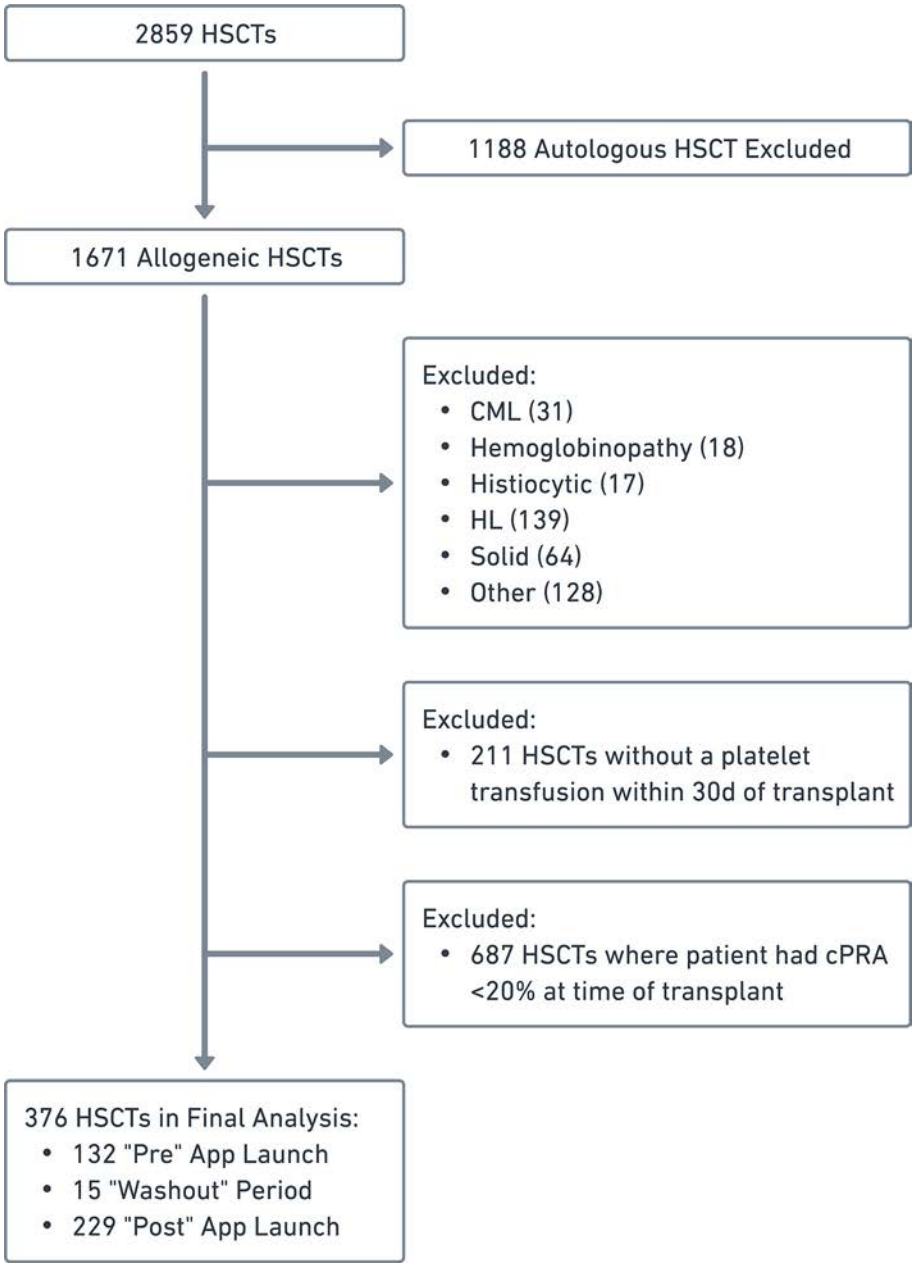

Fig. 3. HSCT patients included in our analysis.

scores were only available on request, and neither the clinicians ordering the platelets, nor the blood bank staff managing the inventory, had ready access to these calculations. By creating a web-application that could calculate cPRA scores in real-time, using the HLA data that were already available, we enabled a new workflow and SOP in our blood bank.

The current operating procedures of our blood bank limit usage of the application for platelet selection to patients with a cPRA $\geq 20\%$. Expanding the set of patients for which the app is used for platelet selection could have multiple benefits. First, it is possible we might see more of an impact with a larger set of patients. Additionally, whereas not formally evaluated, we hypothesize that providing HLA-matched platelets (or at least, providing platelets with some HLA awareness other than first-in–first-out) may prevent HLA sensitization over a longer period.

There are several limitations to our analysis. First, we compared clinical outcomes before the application (2016–2018) to outcomes after the application (2018–2021). Whereas we are not aware of any major HSCT treatment changes, and we attempted to control for intensity of the conditioning regimen, it is possible that the clinical management of HSCT has changed over time in an unmeasured way that would impact the indications for platelet transfusion. Second, whereas the SOP directs blood bank staff to use the application to select the most compatible platelet unit for patients with a cPRA $\geq 20\%$, we do not have a record of why any individual platelet dose was selected for a patient. Finally, whereas most of our platelet transfusions are completely managed at our institution, we do need to purchase doses from a regional blood supplier in some situations; we did not have access to these data for our analysis, though it is a minority of platelet doses.

Whereas the application has been used successfully for many years, there are some updates that we think could make it even better in the future. For example, historic platelet count data from other patients in the post-chemotherapy or post-HSCT window could be used to predict when the platelet count will reach critically low levels following chemotherapy or HSCT and when platelet counts will start to improve. This would allow the blood bank to better anticipate platelet needs and recruit specific local HLA matched platelet donors or order ahead of time from regional blood suppliers. Additionally, including human platelet antigens (HPAs)

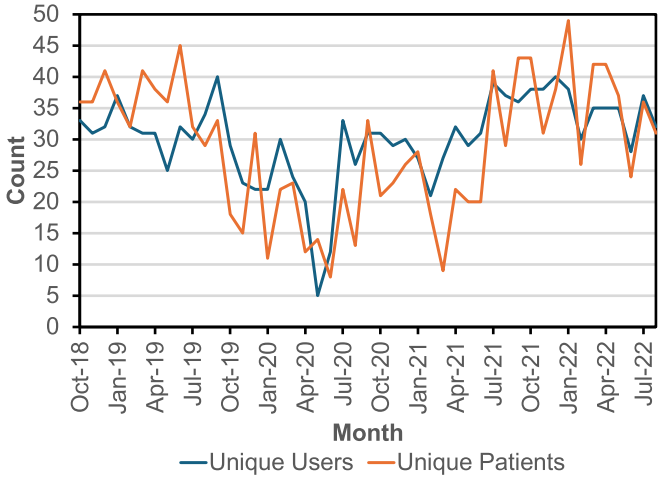

Fig. 4. Application usage over time. Shown is the monthly usage of the application by blood bank clinicians/technologists as well as by number of unique patients loaded into the application that month.

Table 2
Unadjusted and adjusted analysis, 0 = uncomplicated thrombocytopenia course, 1 = complicated thrombocytopenia course, as defined by requiring greater than 4 platelet transfusions or having a 30-day median platelet count <20.

	Unadjusted		Adjusted		
Characteristic	0, N = 192[a]	1, N = 169[a]	OR[b]	95% CI[b]	P-value
Before/After App					
Before	68 (35%)	64 (38%)	—	—	
After	124 (65%)	105 (62%)	0.83	0.53, 1.32	0.43
Disease					
NHL	11 (5.7%)	5 (3.0%)	—	—	
MDS/MPN	50 (26%)	81 (48%)	3.69	1.23, 12.6	0.025
AML	102 (53%)	63 (37%)	1.36	0.45, 4.61	0.60
ALL	29 (15%)	20 (12%)	1.58	0.46, 6.04	0.48
Prep intensity					
RIC	112 (58%)	104 (62%)	—	—	
Myeloablative	78 (41%)	61 (36%)	1.01	0.62, 1.64	0.98
Non-myeloablative	2 (1.0%)	4 (2.4%)	1.71	0.29, 13.6	0.57
HSCT match category					
High	170 (89%)	132 (78%)	—	—	
Low	22 (11%)	37 (22%)	2.31	1.28, 4.27	0.006

[a] n (%).
[b] OR = odds ratio, CI = confidence interval. ALL = acute lymphocytic leukemia, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasms, NHL = non-Hodgkin lymphoma, AML = acute myeloid leukemia, RIC = reduced intensity conditioning.

into the application and typing of our local donors for HPA would allow for managing recipients with either isolated anti-HPA platelet refractoriness or combined with anti-HLA. However, given that HPA and/or anti-HPA are not routinely tested for in donors or recipients, adding this could incur additional costs. However, the app could perhaps enrich for recipients with potential anti-HPA by looking for those who do not respond to HLA-matched platelets. Additionally, the use of high throughput affordable donor typing assays, such as high-density DNA arrays that can simultaneously type large numbers of donors for both HLA and HPA[16] could provide an ample supply of donors for matching.

In conclusion, we built a custom, standards-based software application to improve platelet management processes. By aggregating data from multiple sources, and surfacing these data at the point-of-care, we have created an opportunity for more tailored approaches to platelet transfusion management. We hope to expand our blood bank's SOPs in the future so that the application is used in more clinical scenarios.

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None.

Declaration of competing interest

William Gordon reports a relationship with Great Point Ventures and ZS Consulting that includes: consulting or advisory. Samuel Aronson reports a relationship with Nest Genomics that includes: consulting or advisory. Adam Landman reports a relationship with Abbott Laboratories that includes: consulting or advisory. Melissa Y. Yeung reports a relationship with One Lambda Inc. that includes: consulting or advisory. William J. Lane reports a relationship with One Lambda Inc. and CareDx Inc. that includes: consulting or advisory. William J. Lane has patent with royalties paid to Thermo Fisher Scientific Inc. The other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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