Received: 28 July 2022 | Revised: 19 September 2022 | Accepted: 26 September 2022

DOI: 10.1111/trf.17151

PATIENT BLOOD MANAGEMENT

TRANSFUSION

A data-informed system to manage scarce blood product allocation in a randomized controlled trial of convalescent plasma

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Funding information
Mitacs, Grant/Award Number: Accelerate Program (IT24709); Natural Sciences and Engineering Research Council of Canada, Grant/Award Numbers: Discovery Grant Program (RGPIN-2016-04518), Discovery Grant Program (RGPIN-2022-02999); Canadian Blood Services, Grant/Award Numbers: Blood Efficiency Accelerator Program, Transfusion Medicine Research Program Support

Abstract

Background: Equitable allocation of scarce blood products needed for a randomized controlled trial (RCT) is a complex decision-making process within the blood supply chain. Strategies to improve resource allocation in this setting are lacking.

Methods: We designed a custom-made, computerized system to manage the inventory and allocation of COVID-19 convalescent plasma (CCP) in a multi-site RCT, CONCOR-1. A hub-and-spoke distribution model enabled real-time inventory monitoring and assignment for randomization. A live CCP inventory system using REDCap was programmed for spoke sites to reserve, assign, and order CCP from hospital hubs. A data-driven mixed-integer programming model with supply and demand forecasting was developed to guide the equitable allocation of CCP at hubs across Canada (excluding Québec).

Results: 18/38 hospital study sites were hubs with a median of 2 spoke sites per hub. A total of 394.5 500-ml doses of CCP were distributed; 349.5 (88.6%) doses were transfused; 9.5 (2.4%) were wasted due to mechanical damage sustained to the blood bags; 35.5 (9.0%) were unused at the end of the trial. Due to supply shortages, 53/394.5 (13.4%) doses were imported from Héma-Québec to Canadian Blood Services (CBS), and 125 (31.7%) were transferred between CBS regional distribution centers to meet demand. 137/349.5 (39.2%) and 212.5 (60.8%) doses were transfused at hubs and spoke sites, respectively. The mean percentages of total unmet demand were similar across the hubs, indicating equitable allocation, using our model.

Conclusion: Computerized tools can provide efficient and immediate solutions for equitable allocation decisions of scarce blood products in RCTs.

KEYWORDS

convalescent plasma, data-driven optimization, demand forecasting, mathematical models, randomized controlled trials, resource allocation, scarce blood product

1 | INTRODUCTION

Blood product allocation in the blood supply chain requires complex decisions involving blood collection, processing, transportation with the maintenance of the cold chain, inventory, pre-transfusion manipulation/testing, and transfusion from donors to patients.[1–4] Diverse types of decisions need to be made, including determining the location of blood centers, the capacity of collection processes, inventory policies, issuing policies, and emergency ordering policies.[5–8] Shortage and wastage of blood products may result in increased costs, delays in treatments, untreated patients, and even deaths.[9,10] Hence, designing and optimizing the decision processes for scarce blood product allocation is vital.

Blood products are involved in large and diverse randomized controlled trials (RCTs).[11–15] COVID-19 Convalescent Plasma (CCP) is collected from recently recovered donors and contains antibodies against the SARS-CoV2 virus. CCP has been studied as an experimental transfusion therapy in a number of RCTs worldwide.[16–22] Recruiting and retaining CCP donors was challenging,[23] and led to shortages in supply. One of these studies, the randomized, open-label trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness (CONCOR-1) was an RCT involving 72 academic and community sites across Canada, the United States, and Brazil.[17] A number of challenges were encountered when making decisions on CCP allocation in the trial: (i) limited CCP supply due to the difficulties in donor identification and recruitment, (ii) geographically dispersed hospital sites and blood distribution centers, (iii) heterogeneous and variable demand for CCP, highly impacted by external factors such as government responses and the transmission dynamics of COVID-19, (iv) limited historical data to inform CCP demand and supply, (v) specific clinical requirements, such as ABO blood group compatibility, and (vi) the need for near real-time allocation decisions at the time of randomization.

While seeking long-term plans to increase blood donations, strategies to improve allocation decisions under limited and variable supply provide more efficient and immediate solutions for such RCT settings. To aid decision-making for CCP allocations, we built computerized tools to address the challenges in the CONCOR-1 trial. This paper describes the tools and their potential use in clinical trials or other settings that involve the allocation of scarce blood products.

2 | METHODS

2.1 | Problem setting

A customized CCP allocation and inventory management system was developed for the multi-site RCT, CONCOR-1,[24] conducted between May 2020 and January 2021. Patients were recruited and randomized 2:1 to receive one CCP dose of 500-ml (from one single-donor unit of 500 ml or 2 units of 250 ml from 1 to 2 donors) or standard of care (SOC). The trial included 52 active hospital sites across Canada with 38 sites supplied by 8 regional Canadian Blood Services (CBS) distribution centers and 14 sites supplied by Héma-Québec. The first CCP unit for the trial was collected on April 24, 2020, and a total of

940 patients were randomized between May 14, 2020 and January 29, 2021.[17]

One of the key eligibility criteria required real-time CCP inventory information before randomizing a patient: 500-ml of ABO-compatible CCP from a single-donor unit of 500 ml or 2 units of 250 ml from 1 to 2 donors was available locally within 24 h prior to randomization.[24] The CCP distribution team (comprised of study investigators, a data scientist, and research staff) were responsible for managing and distributing CCP units centrally based on live inventory. Two other RCTs, REMAP-CAP[25] and CONCOR-KIDS,[26] utilized the same CCP electronic inventory system that we developed for the CONCOR-1 trial. A list of principles was established to ensure equitable CCP allocation: (i) CCP units for Canadian sites outside of Québec would be collected by CBS as a national inventory to be distributed based on needs. Québec sites were supplied by Héma-Québec. Transferring CCP units from Héma-Québec was a contingency management strategy for CBS supply shortages; (ii) CCP units should be equitably distributed across geographic regions, study sites, and clinical trials; (iii) distribution of CCP inventory should be controlled centrally by the CCP distribution team (to ensure equitable and effective operations).

The outcomes of this study were (i) two forecasting accuracy measures: Root Mean Square Error (RMSE) which quantifies the absolute errors between predicted and observed values, and Mean Absolute Percentage Error (MAPE) which calculates the average percentage error between predicted and observed values; (ii) the resource allocation performance measured by mean unmet demand ($\overline{u}_T$) and mean percentage of total unmet demand over total demand ($\overline{z}_T$). The equations for RMSE, MAPE, $\overline{u}_T$, and $\overline{z}_T$ are presented in Appendix A (Appendix S1).

2.2 | Hub and spoke distribution model

A hub-and-spoke distribution model[27] was used to enable real-time inventory monitoring and availability of CCP for randomization. CCP was a scarce product, especially in the early stages of the COVID-19 pandemic. To ensure doses (500 ml per dose) were available for transfusion when a patient was randomized to the CCP arm, it was important to allow study sites real-time access to CCP inventory. This functionality was not available under the existing infrastructure between CBS and hospital sites. A hub-and-spoke model has been shown to be efficient, providing care to even the most rural areas.[28,29] A hub-and-spoke structure was established for CONCOR-1 where CCP units were distributed from CBS regional distribution centers to hospital hubs for subsequent CCP allocation to patients (Figure 1). The final hub locations were administrative decisions based on agreements between the CONCOR-1 study team and hospital sites. CCP units could be transferred between CBS regional distribution centers. When a CCP unit was allocated in a hospital hub, it remained in the hub inventory until utilization. Re-distribution between hospital hubs was only considered in emergency situations, as evaluated by the CCP distribution team.

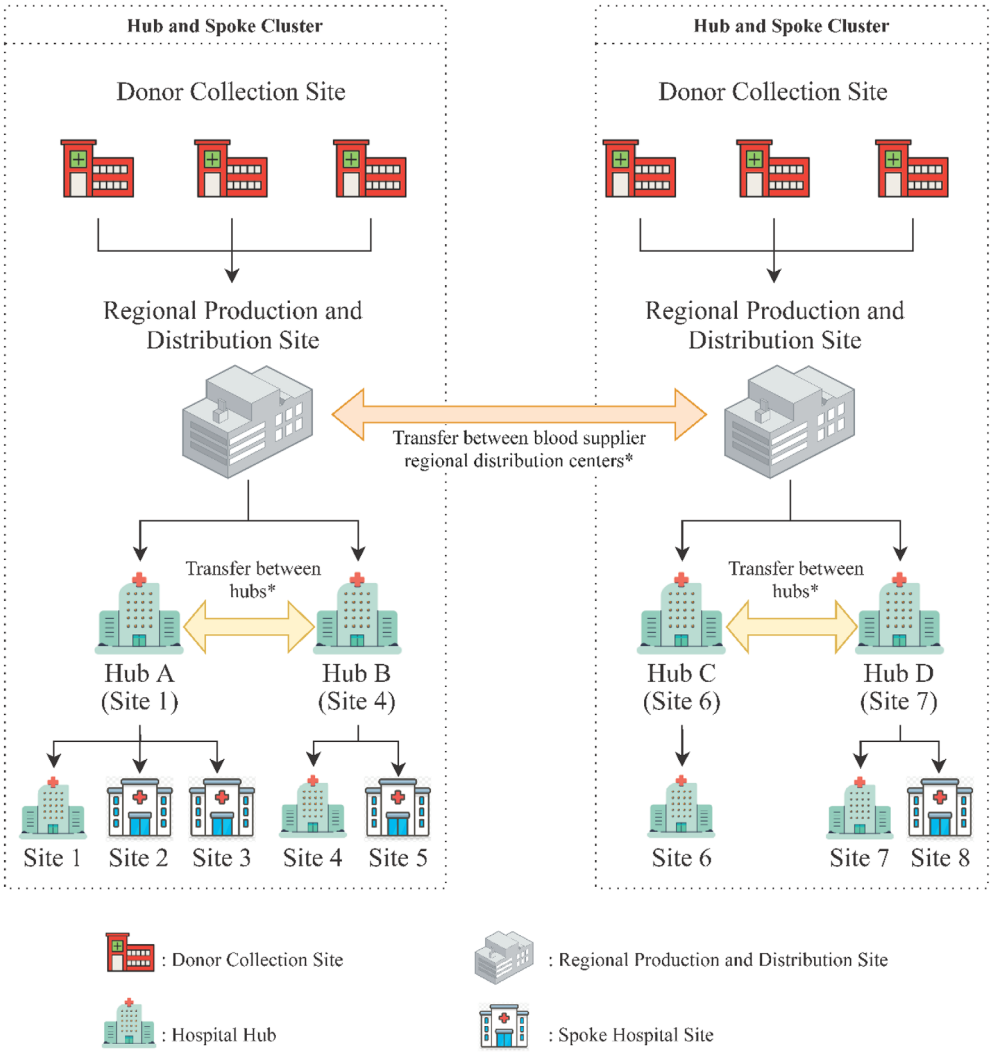
2.3 | REDCap tools to reserve, assign, and order CCP

A live CCP inventory system using REDCap[30] was programmed for spoke sites to reserve, assign, and order CCP units from a hospital hub and was used by the CONCOR-1 team throughout the trial. This inventory tool was embedded in the REDCap platform through uniform resource locator (URL) links and operated automatically during data collection. The process flow diagram is shown in Figure 2 and described in Appendix B (Appendix S1). Training for site research coordinators was provided before site activation.[31] A web-based tool was developed to request CCP from CBS for hospital hubs and to monitor hub inventories. This inventory monitoring tool was managed by the CCP distribution team. The tool made the demand and supply data transparent among CBS and hospital hubs to enable efficient inventory management.

2.4 | Models to guide equitable CCP allocation

At the beginning of the trial, no historical CCP demand and supply data were available. We refined a simulation model to forecast short-term CCP demand and supply based on the COVID-19 Hospital Impact Model for Epidemics (CHIME). The CHIME model uses a Monte Carlo simulation instantiation of a susceptible, infected, removed (SIR) model[32] with a one-day cycle up to 30 days.[33] We added a number of parameters to simulate the trial enrolment, CBS supply, and hub demand by ABO blood groups (based on population prevalence estimates in Canada), and then stored the simulated results to capture the inventory and planned CCP allocation at each hub. Details of the simulation model can be found in Appendix C (Appendix S1).

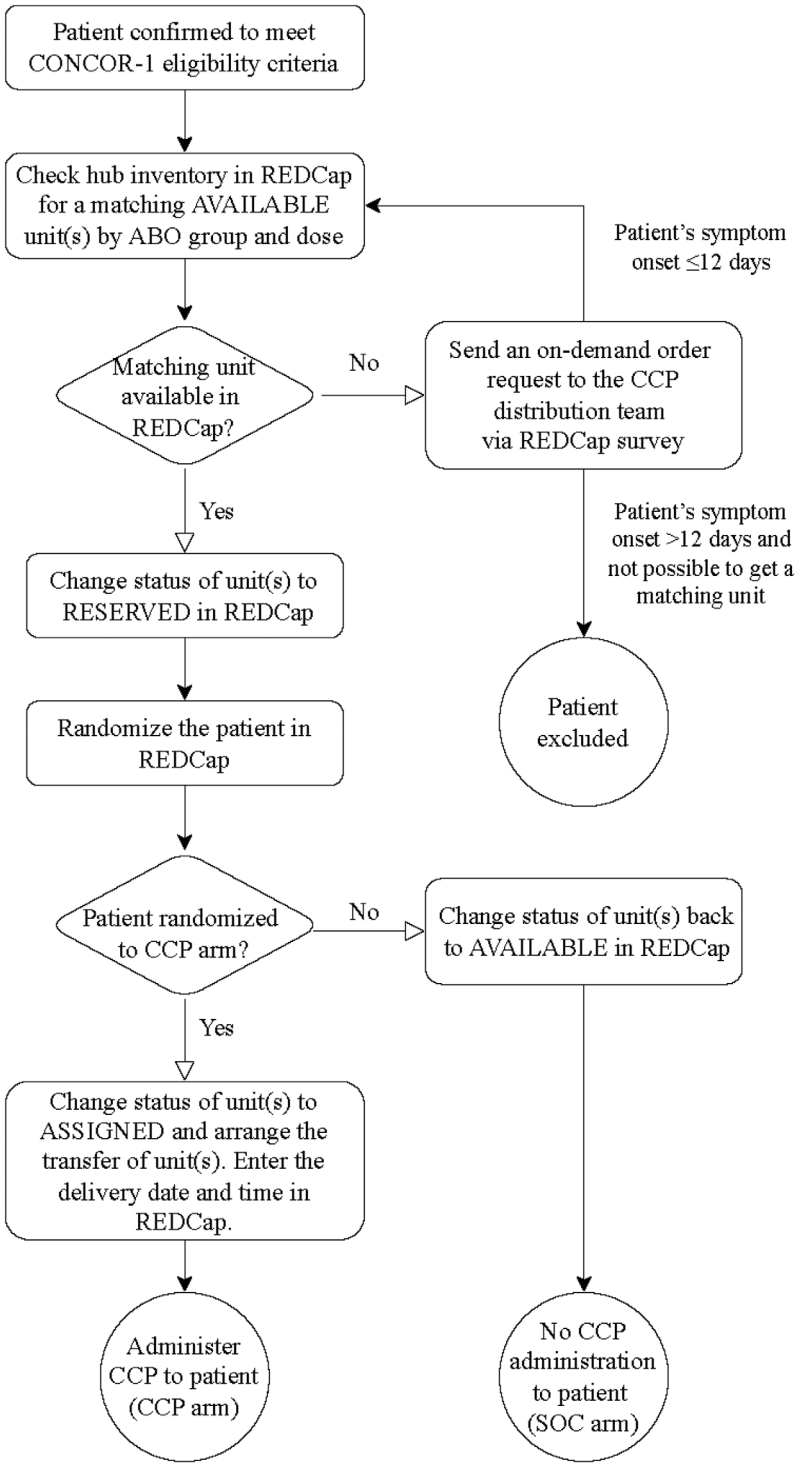
When more data became available, we developed a data-driven mixed-integer programming (MIP) model for



*Under the existing blood supply chain at Canadian Blood Services (CBS), transfers of blood products were conducted between regional blood distribution centers. Transfers between hospital hubs can be made but were not desired due to transportation limitations. Transfers between spoke hospital sites were not allowed.

FIGURE 1 Hub and spoke distribution model. *Under the existing blood supply chain at Canadian Blood Services (CBS), transfers of blood products were conducted between regional blood distribution centers. Transfers between hospital hubs can be made but were not desired due to transportation limitations. Transfers between spoke hospital sites were not allowed. [Color figure can be viewed at wileyonlinelibrary.com]

real-time multi-location resource allocation with sparse data.[34] The model has two components: (a) real-time supply and demand forecasting with error analysis and (b) resource allocation optimization by maximizing a notion of fairness among hospital hubs. We used multivariate adaptive regression splines (MARS)[35] to forecast the supply and demand in week $t+1$ using all historical data up to week t. To improve forecasting accuracy, the forecasting error for week $t+1$ was estimated using an autoregressive (AR) model. The final forecasts with error correction in week $t+1$ were the forecasts from MARS plus the estimated errors from the AR model.[36–38] Separate models were built to forecast supply and demand using the same method (MARS+AR). In the resource allocation optimization step, an objective function was defined to capture our notion of fairness: minimizing the highest ratio of unmet demand across all hospital hubs. In other words, the goal of the optimization model was to reduce the variation of potential hospital hubs' unmet demand due to limited supply. An ABO compatibility matrix between donor and recipient for plasma transfusions[39] was embedded in the optimization model. Although group-AB plasma is the universal donor plasma, the group-AB population is the smallest; hence, group-AB CCP doses were not prioritized to be used for group-A or O patients. In the primary model, we adopted the same ABO compatibility policy in CONCOR-1 that when ABO-identical doses were unavailable, group-A CCP could be given to group-O recipients, group-AB CCP could be given to group-B recipients, and patients with A or AB blood group would wait for their ABO-identical doses. The number of doses by ABO blood groups to be allocated at each



- CCP: convalescent plasma; SOC: standard of care.
- The REDCap metadata with data collection instruments and a training video can be found in the supplemental materials.

FIGURE 2 Reserving and assigning CCP doses using REDCap in the CONCOR-1 trial. CCP, convalescent plasma; SOC, standard of care. The REDCap metadata with data collection instruments and a training video can be found in the supplemental materials.

hospital hub in week $t+1$ was the output from the optimization model. Technical details can be found in Section 3 of our paper.[34]

With the proposed allocation decision, the team placed orders to CBS for CCP distribution across hospital hubs. The overall decision process for CCP allocation is

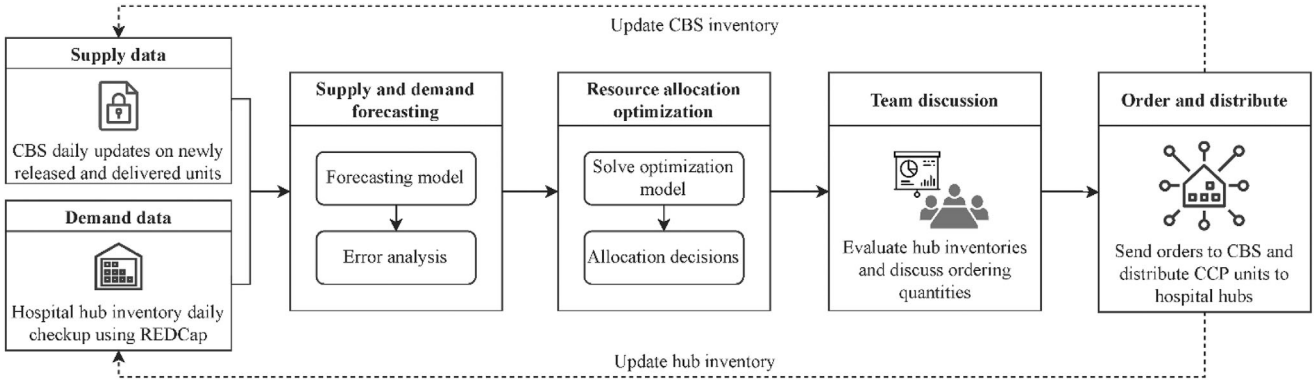


FIGURE 3 CCP allocation decision-making process

illustrated in Figure 3. Both models were programmed using Python Version 3.8.[40]

2.5 | Statistical analysis

For descriptive analysis, statistics using mean and standard deviation (SD) and/or median and interquartile range (IQR) on CCP allocation, demand, end-of-week inventory, wastage, and unused doses were presented for each hospital hub. We reported the statistics based on complete study products in CONCOR-1,[24] that is, 500-ml CCP doses, where a half dose refers to a 250-ml unit of CCP. Bar charts were used to describe the number of doses by ABO blood groups. The proportions of doses with delays from CCP assignment to transfusion for randomized patients at hospital hubs and spoke sites were calculated and compared using two-sample test for proportions. The difference in proportions with a 95% confidence interval (CI) and *p*-value was reported. A *p*-value less than .05 was considered as statistically significant. An alluvial diagram was used to illustrate the flow of CCP distributions from blood suppliers to hospital hubs. The RMSE, MAPE, mean unmet demand, and mean percentage of total unmet demand were reported. The standard errors (SEs) calculated based on 300 simulation samples[34] were reported for mean unmet demand and mean percentage of total unmet demand. A sensitivity analysis was performed considering the ABO-identical transfusion policy to evaluate the impact of ABO compatibility on CCP allocation.

3 | RESULTS

Among the 38 hospital sites supplied by CBS, 18 hospital hubs were identified and activated from May 2020 to January 2021. The median (IQR) number of spoke sites per hub was 2 (1, 3). There were 275 distributions with a total of 394.5 500-ml CCP doses (769 units of 250 ml and 10 units of 500 ml) to the 18 hospital hubs on 134 unique dates, with 39 (14.2%) distributions on weekends. The median (IQR) number of 500-ml doses distributed per hub was 16 (7, 24). The median (IQR) duration from CCP order date to the received date by hospital hubs was 1 (0, 1) day. Among the 394.5 distributed doses, 349.5 (88.6%) were transfused, 9.5 (2.4%) were wasted due to damage or leakage, and 35.5 (9.0%) doses remained in inventory at the end of the CONCOR-1 trial.

Due to low supply, 53 out of 394.5 (13.4%) doses were imported from Héma-Québec to CBS in the first and last months of the study period (Appendix D (Appendix S1) Figure 1), where 14 (26.4%) were group O, 15 (28.3%) were group A, 10 (18.9%) were group B, and 14 (26.4%) were group AB. The remaining 341.5 (86.6%) doses were supplied by CBS. Besides the units from Héma-Québec, 125 (31.7%) doses were transferred between CBS regional distribution centers to fulfill demand in a different province (Figure 4). With these cross-province transfers, there were in total 5 doses in shortage (4 group-AB doses at one hospital hub and three-spoke sites, and 1 group-B dose at one spoke site) that prevented patients from enrolling in the trial.

Among the 349.5 transfused doses, 112.5 (32.2%) were group O, 157 (44.9%) were group A, 41 (11.7%) were group B, and 39 (11.2%) were group AB (Figure 5). The CCP demand distribution by ABO blood groups differed significantly from the Canadian blood group distribution (46% group O, 42% group A, 9% group B, and 3% group AB),[41] indicating the large mismatch between demand and expected supply, especially for rare blood groups. Table 1 presents the summary statistics of CCP allocation, demand, end-of-week inventory, wastage, and unused doses for hospital hubs (statistics by ABO blood groups can be found in Appendix D (Appendix S1) Table 1). 334 (95.6%) doses were transfused in

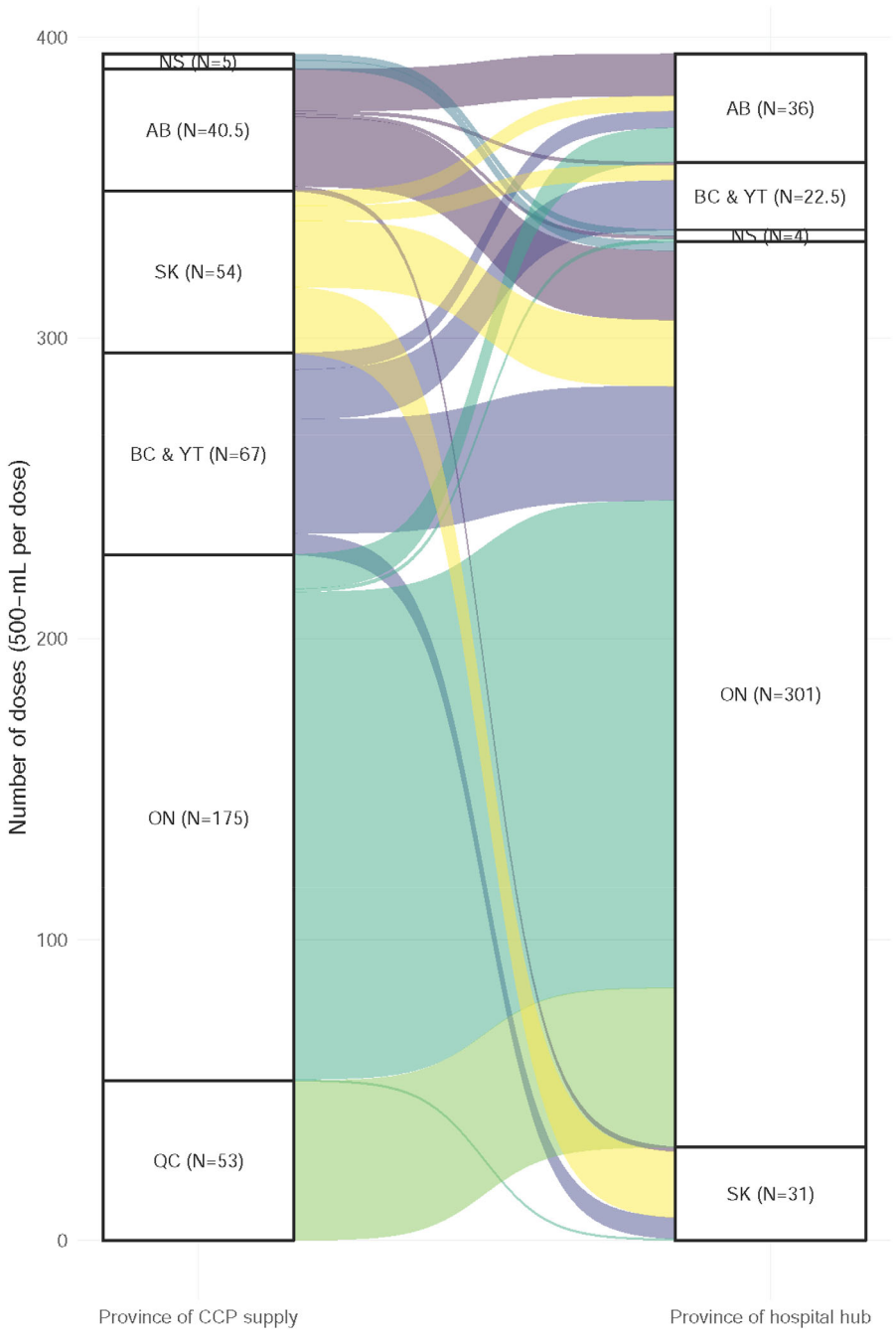


FIGURE 4 Alluvial diagram of cross-province CCP distributions from the provinces of regional blood distribution centers to the provinces of hospital hubs in the CONCOR-1 trial. AB, Alberta; BC & YT, British Columbia & Yukon Territories; NS, Nova Scotia; ON, Ontario; SK, Saskatchewan; QC, Québec. [Color figure can be viewed at wileyonlinelibrary.com]

AB: Alberta; BC & YT: British Columbia & Yukon Territories; NS: Nova Scotia; ON: Ontario; SK: Saskatchewan; QC: Québec.

CONCOR-1, and 15.5 (4.4%) were transfused in REMAP-CAP and CONCOR-KIDS. 137 (39.2%) doses were transfused at hospital hubs, and 212.5 (60.8%) doses were transfused at spoke sites; 6/137 (4.4%) doses at hubs, and 13/212.5 (6.1%) doses at spoke sites had a delay of more than 1 day from CCP assignment to transfusion. No significant difference in the proportions of doses with delays between the hubs and spoke sites were found (difference in proportions = −1.7%; 95% CI, −7.0% to 3.6%; $p = .647$).

3.1 | Supply and demand forecasting

The forecast accuracy using MARS+AR (Figure 6) was determined by comparing the estimated cumulative supply/demand with the actual cumulative supply/demand over 22 weeks from August 31, 2020 to January 29, 2021. Considering the aggregate supply and demand forecasting across all hubs, the RMSE and MAPE were 7.0 and 3.7% for demand forecasts, and 10.7 and 6.1% for supply forecasts. The overall supply forecasts had more errors

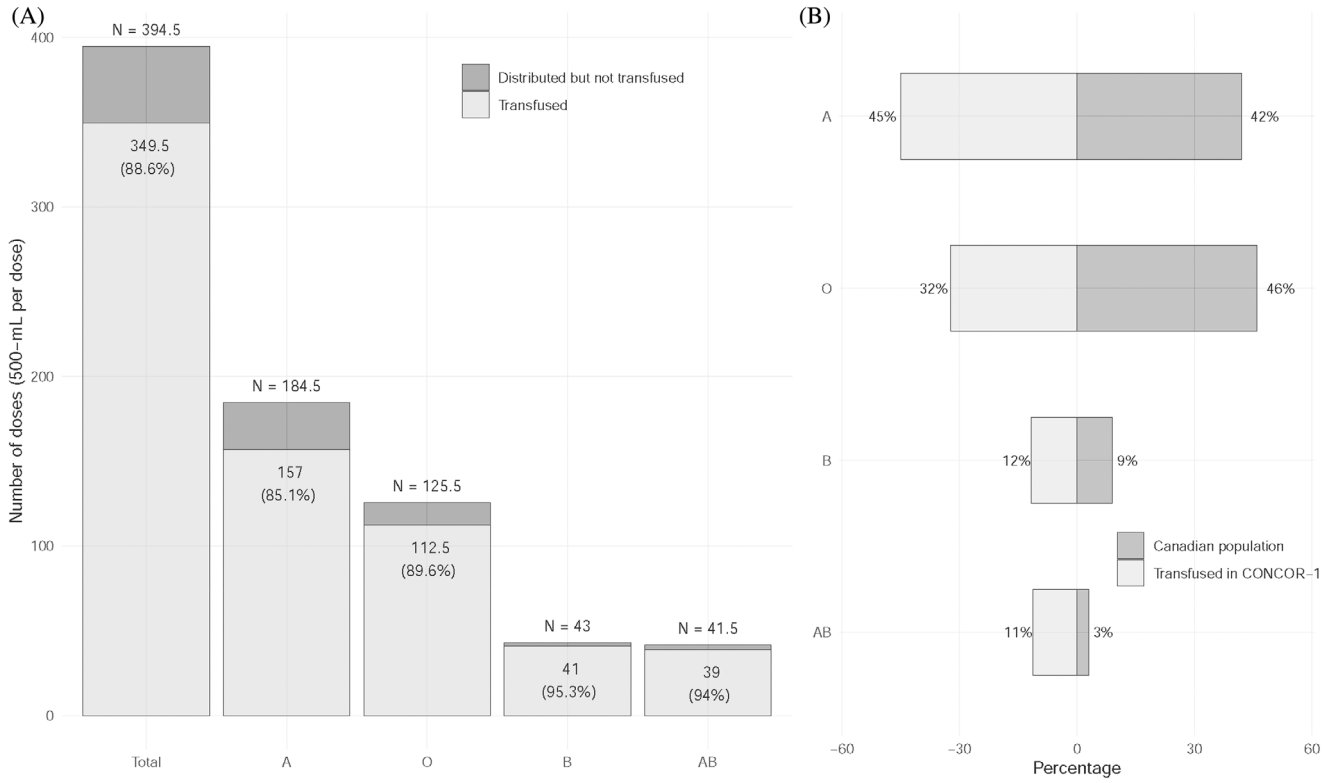


FIGURE 5 Bar charts of CCP doses by ABO blood group: (A) doses distributed, transfused, wasted/remained in inventory; (B) blood group distributions for transfused patients in CONCOR-1 and Canadian population

since the cumulative supply data had a higher degree of nonlinearity (Figure 6). However, for hub-specific predictions, demand forecasting accuracy varied significantly between hubs because of the heterogeneous demand patterns for different hubs and regions, with MAPEs ranging from 7.3% to 27.9%. The order of forecasting errors from largest to smallest by blood groups was B > AB > A > O for demand forecasts, AB > O > B > A for supply forecasts. The intersections between cumulative supply and cumulative demand curves in Figure 6 indicated the time points of shortages. CCP transfers from Héma-Québec were triggered when the two curves approached each other.

3.2 | CCP allocation optimization

Table 2 reports the CCP allocation in the CONCOR-1 trial based on the data-driven MIP model using forecasted supply and demand and the actual allocation after final team decisions. The mean unmet demand and mean percentage of total unmet demand were affected by the relative forecasted demand proportions and forecasted demand variations between hubs. The larger the demand proportion relative to other hubs, the larger the mean unmet demand and mean percentage of total unmet demand; the larger the demand variation relative to other hubs, the larger the SEs of the mean unmet demand and mean percentage of total unmet demand. When comparing the mean unmet demand and mean percentage of total unmet demand between the data-driven MIP model and the actual allocations in the trial, further improvements can be achieved through the MIP allocations: (i) the mean unmet demand under the MIP model was lower for most hubs; (ii) the mean percentages of total unmet indicated the allocations were fairer under the MIP model.

For the sensitivity analysis, the allocation results between the model with the CONCOR-1 compatibility matrix and the model with the ABO-identical transfusion policy are shown in Appendix D (Appendix S1) Table 2. The mean unmet demand and mean percentage of total unmet demand were significantly reduced by the ABO-identical policy for two hubs (highlighted in red), and were similar for the other hubs.

4 | DISCUSSION

In this study, we described the three components for CCP allocation decision-making in the CONCOR-1 trial—a multi-site RCT testing the effect of a scarce, experimental

TABLE 1 CCP allocation, demand, end-of-week inventory, wastage, and unused doses by hospital hub

		Allocation			Demand			End of week inventory			
Hub	Province	Total	Mean (SD)	Median (IQR)	Total	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Total remain	Total wasted
Hub1	ON	128	3.4 (3.4)	3 (0–6)	121.5	3.2 (3.5)	2 (0–5)	10.2 (3)	11 (8–12)	1.5	5
Hub2	ON	41.5	1.1 (1.5)	0 (0–2)	39.5	1 (1.2)	1 (0–2)	4.2 (2.2)	4 (3–6)	1	1
Hub3	ON	36	0.9 (1.7)	0 (0–1)	33	0.9 (1.4)	0 (0–2)	3.4 (1.6)	4 (2–4)	0	3
Hub4	ON	26	0.7 (1.1)	0 (0–1)	23.5	0.6 (1)	0 (0–1)	4.6 (2.9)	4 (2–9)	1.5	1
Hub5	AB	23.5	0.6 (1.2)	0 (0–1)	21	0.6 (0.9)	0 (0–1)	3.5 (2.7)	2 (2–6)	0.5	2
Hub6	ON	23	0.6 (1.1)	0 (0–1)	20	0.5 (0.9)	0 (0–1)	4.5 (1.9)	4 (3–6)	0	3
Hub7	ON	17.5	0.5 (0.7)	0 (0–1)	16	0.4 (0.7)	0 (0–1)	3.4 (1.6)	4 (2–5)	0.5	1
Hub8	ON	17.5	0.5 (0.9)	0 (0–1)	14	0.4 (1.1)	0 (0–0)	3.7 (1.5)	4 (3–5)	1.5	2
Hub9	SK	15.5	0.4 (1)	0 (0–0)	13.5	0.4 (1)	0 (0–0)	2 (1.4)	2 (1–3)	0	2
Hub10	AB	12.5	0.3 (0.7)	0 (0–0)	11	0.3 (0.6)	0 (0–0)	2.6 (1.7)	3 (1–4)	0.5	1
Hub11	SK	15.5	0.4 (1.1)	0 (0–0)	9	0.2 (0.9)	0 (0–0)	1.2 (2.2)	0 (0–2)	1	5.5
Hub12	BC & YT	10	0.3 (0.6)	0 (0–0)	9	0.2 (0.6)	0 (0–0)	3.9 (2.3)	5 (2–5)	0	1
Hub13	ON	9.5	0.2 (0.6)	0 (0–0)	8	0.2 (0.5)	0 (0–0)	2.4 (0.8)	3 (1–3)	0.5	1
Hub14	BC & YT	6	0.2 (0.5)	0 (0–0)	4	0.1 (0.3)	0 (0–0)	1.6 (1)	2 (0–3)	1	1
Hub15	NS	4	0.1 (0.4)	0 (0–0)	2	0.1 (0.2)	0 (0–0)	1.2 (1.2)	1 (0–2)	0	2
Hub16	BC & YT	3	0.1 (0.4)	0 (0–0)	2	0.1 (0.2)	0 (0–0)	0.4 (0.8)	0 (0–1)	0	1
Hub17	BC & YT	3.5	0.1 (0.4)	0 (0–0)	1.5	0 (0.2)	0 (0–0)	1.5 (1)	2 (0–2)	0	2
Hub18	ON	2	0.1 (0.3)	0 (0–0)	1	0 (0.2)	0 (0–0)	0.6 (0.9)	0 (0–2)	0	1
All combined		394.5	10.4 (7.3)	9 (4–16)	349.5	9.2 (9.1)	5 (2–16)	54.8 (20.1)	56 (45–70)	35.5	9.5

Note: Numbers in the table represent the numbers of 500-ml CCP doses. Mean (SD) and median (IQR) were calculated over 38 weeks for each hospital hub during the entire study period. Total allocation = Total demand + Total wasted + Total remaining. The 53 doses transferred from Héma-Québec were included in the table. End of week inventory represents the number of doses on hand at the end of each week that reflects the holding inventory to prevent shortages. In general, larger hubs with higher demands hold more inventory than small hubs. AB, Alberta; BC & YT, British Columbia & Yukon Territories; NS, Nova Scotia; ON, Ontario; SK, Saskatchewan.

transfusion therapy for patients with COVID-19 where the blood products were donated by COVID-19-recovered patients. A hub-and-spoke distribution model was designed to handle geographically disparate sites with limited supply and variable demand. A live CCP inventory system was programmed in REDCap with functions to reserve/assign/order units at hospital sites and to generate reports for inventory monitoring. Two mathematical models were constructed for real-time CCP allocation: the CHIME model was applied at the beginning of the trial when supply and demand data were not available, and a data-driven MIP model was developed when data were collected. A user-friendly interface was programmed for the data-driven MIP model, allowing for ease of use for research staff. With these tools, the CONCOR-1 team was able to (1) perform real-time inventory checking to ensure the compliance of their transfusion protocol, (2) obtain auto-computed supply and demand forecasts, and CCP allocation suggestions for the coming week, and (3) monitor and update hub inventory levels centrally. We, therefore, achieved equitable CCP distributions across hospital hubs with low wastage (2.4% of all distributed doses).

There is a lack of published research that provides insights into blood supply and demand management for scarce products in clinical trials. As a randomized intervention, poor linkage across blood donor recruitment, inventory management, and the randomization process can raise biases. For instance, performance and attrition bias[42] may increase due to supply shortage for rare blood groups. Inefficient supply chain management also affects trial participant recruitment and creates challenges in resource equity, especially in multi-site studies. Such challenges were magnified by the COVID-19 pandemic due to heterogeneous disease spread, variable and waning antibody in donors with previous COVID-19 infections, and donor recruitment barriers. In particular, public health privacy restrictions on releasing patient information caused significant supply differences between Héma-Québec (which had a contact list of

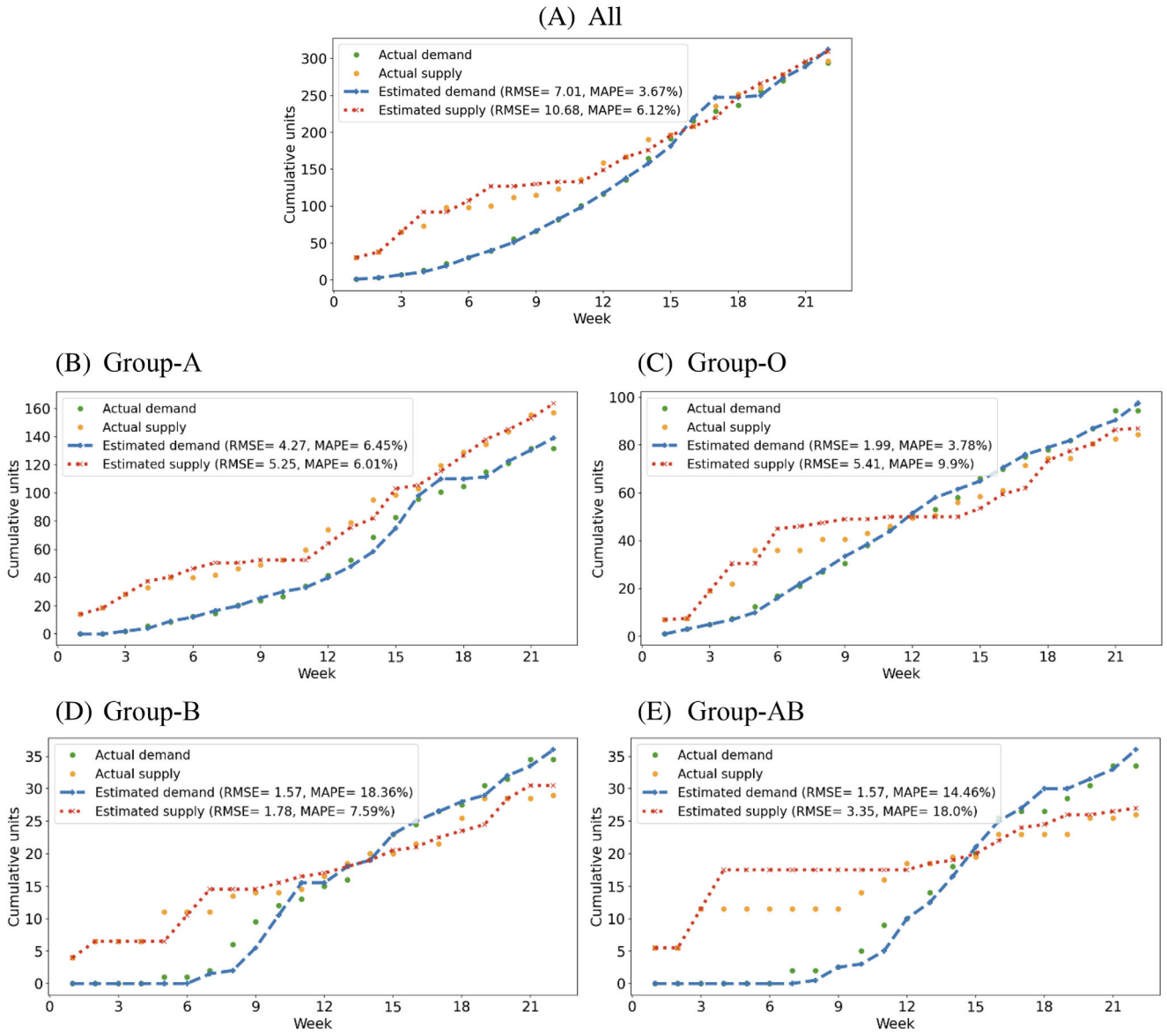


FIGURE 6 Cumulative weekly supply and demand forecasts using MARS+AR for all hubs from August 31, 2020 to January 29, 2021 [Color figure can be viewed at wileyonlinelibrary.com]

recovered patients in Québec) and CBS (which was not permitted access to contacts of recovered patients). Our experience shows that the three components (hub-and-spoke distribution model, live CCP inventory system, and mathematical models for CCP allocation) together ensured the efficiency and equitability of CCP allocation in the RCT. Although there were significant differences between the supply and demand of blood group-specific CCP units, only five patients were unable to enroll in the study due to ABO-compatible plasma shortage, representing 0.5% of the total excluded patients in CONCOR-1.[17] Impending shortages were recognized in advance and resolved within the inventories of CBS distribution centers and transfers from Héma-Québec. This can only be achieved through a transparent supply and demand management system.

There have been many applications and tools developed to forecast infections, hospitalizations, and deaths due to COVID-19 using compartmental models.[43–48] In the early stages of the RCT, we also applied the CHIME model to forecast the number of hospitalized COVID-19 patients. We found the compartmental model had significant limitations given the model assumptions and was highly affected by the variability of data.[49] Moreover, a large number of parameters were required to build the compartmental model, and accurately updating all these parameters in a timely manner was challenging. Therefore, supply and demand forecasting models were developed when data became available. Time series and machine learning models are widely used for demand forecasting.[6,50,51] Such methods

TABLE 2 CCP allocation based on the data-driven MIP model and actual CCP allocation in CONCOR-1 from August 31, 2020 to January 29, 2021

Hub	Total actual demand	Total forecasted demand using MARS+AR	Forecasting accuracy		Allocation using the data-driven MIP model		Actual allocation in CONCOR-1	
			RMSE	MAPE (%)	$\bar{u}_T \pm$ SE	$\bar{z}_T \pm$ SE(%)	$\bar{u}_T$	$\bar{z}_T$ (%)
Hub-A	105	110.5	3.00	15.12	7.63 ± 0.19	7.27 ± 0.18	27.00	25.71
Hub-B	74	77	2.97	11.32	5.97 ± 0.20	8.07 ± 0.27	20.00	27.02
Hub-C	30	29.5	1.76	7.31	1.21 ± 0.05	4.03 ± 0.16	5.00	16.67
Hub-D	29	30	1.74	12.87	1.65 ± 0.10	5.70 ± 0.34	1.50	5.17
Hub-E	26	28.5	2.33	21.70	1.52 ± 0.08	5.85 ± 0.30	4.50	17.31
Hub-F	17.5	20.5	2.64	27.91	0.42 ± 0.03	2.38 ± 0.15	1.00	5.71
Hub-G	12.5	10.5	1.06	16.07	0.93 ± 0.03	7.47 ± 0.27	3.00	24.00

Note: Since the demands were sparse for small hubs, further consolidation of hospital hubs was conducted for CCP allocation optimization: Hub-A: Hub1; Hub-B: Hub3, 4, 6, 13; Hub-C: Hub2; Hub-D: Hub5, 10; Hub-E: Hub7, 8; Hub-F: Hub9, 14; Hub-G: Hub12, 16, 17. The consolidation was based on geographical region, CBS distribution route, and hospital size. Hubs 11 and 18 were only activated to hold CCP inventory within the last 3 months prior to the termination of the trial. Hub 15 represented the only participating hospital as its own hub in Nova Scotia and had extremely low demand (two doses as shown in Table 1). Thus, Hubs 11, 15, and 18 were excluded from this table. The forecasting accuracies were from the demand forecasting models for the demands of all blood groups. Forecasting accuracies by blood group can be found in the reference.[34] The allocation results using the data-driven MIP models in this table were generated based on the CONCOR-1 compatibility matrix. The allocation results under the ABO-identical policy can be found in Appendix D (Appendix S1) Table 2.

require a reasonable sample size, for example, the rule of thumb for ARIMA is at least 50 but preferably more than 100 observations.[52] However, we only had 22 weekly supply and demand data points. We found piecewise linear models[53–55] to be an appropriate alternative, as our data were limited, sparse, and nonstationary with structural shifts (e.g., waves of COVID-19 and government restrictions).

"Fairness" can be defined in different ways for health resource allocation.[56–58] In our problem setting—a multisite RCT with limited intervention supply, the guiding principle was to ensure that all hospital hubs had equal opportunity to fulfill their demands. Hence, we defined our notion of fairness as minimizing the highest ratio of unmet demand across all hospital hubs. This can be modified to capture notions of fairness that are appropriate for other settings, for example, maximizing treatment effects.[58]

Using a sensitivity analysis, we found that the ABO compatibility policy plays a role in CCP allocation. It is well known that ABO-compatible plasma is required to ensure safe transfusion. With limited supply, the standard ABO compatibility policy with AB plasma as the universal donor may result in unfairness to group-AB recipients. To compensate, a modified compatibility policy was used in the CONCOR-1 trial. We found that under the CONCOR-1 compatibility matrix, excess O and B demand was compensated by A and AB units, respectively. However, as the supply and demand by blood group were imbalanced (Figure 5), and the supply of AB units was the lowest, this policy further increased the chance of shortages for AB units, resulting in higher unmet demand than the model under the ABO-identical transfusion policy. Hence, the ABO-identical policy may be a better choice when forecasting errors and imbalanced supply and demand for ABO blood groups are inevitable.

In summary, we demonstrated that a customized inventory management system for CCP met the needs of patients randomized in the CONCOR-1 trial. The tools can be used to improve the allocation of scarce blood products to ensure that demand is met in a timely, equitable fashion across a large geographical region. With trials being planned worldwide to evaluate both whole blood and cold-stored platelets, this model could be harnessed to improve trial logistics and feasibility.

FUNDING INFORMATION

This study was funded by Dr. Li's Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant Program (RGPIN-2022-02999), Dr. Down's NSERC Discovery Grant Program (RGPIN-2016-04518), and the Canadian Blood Services Transfusion Medicine Research Program Support Award to Dr. Arnold at the McMaster Centre for Transfusion Research. The funding for the development of the user interface was supported by Dr. Shih's Canadian Blood Services Blood Efficiency Accelerator Program and the Mitacs Accelerate Program (IT24709).

CONFLICT OF INTEREST

Michelle Zeller has received research support from Canadian Blood Services.

Jeannie Callum has received research support from Canadian Blood Services and Octapharma.

Donald Arnold has received research support from Canadian Blood Services.

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REFERENCES

1. Williamson LM, Devine DV. Challenges in the management of the blood supply. Lancet. 2013;381(9880):1866–75. https://doi.org/10.1016/S0140-6736(13)60631-5
2. Torrado A, Barbosa-Póvoa A. Towards an optimized and sustainable blood supply chain network under uncertainty: a literature review. Clean Logist Supply Chain. 2022;3(100028):1–25. https://doi.org/10.1016/j.clscn.2022.100028
3. Yousefi Nejad Attari M, Pasandideh SHR, Akhavan Niaki ST. A hybrid robust stochastic programming for a bi-objective blood collection facilities problem (case study: Iranian blood transfusion network). J Ind Prod Eng. 2019;36(3):154–67. https://doi.org/10.1080/21681015.2019.1645747
4. Williams EP, Harper PR, Gartner D. Modeling of the collections process in the blood supply chain: a literature review. IISE Trans Healthc Syst Eng. 2020;10:200–11. https://doi.org/10.1080/24725579.2020.1776426
5. Soares HLF, Arruda EF, Bahiense L, Gartner D, Amorim FL. Optimisation and control of the supply of blood bags in hemotherapic centres via Markov decision process with discounted arrival rate. Artif Intell Med. 2020;104:101791. https://doi.org/10.1016/j.artmed.2020.101791
6. Li N, Chiang F, Down DG, Heddle NM. A decision integration strategy for short-term demand forecasting and ordering for red blood cell components. Oper Res Health Care. 2021;29:100290. https://doi.org/10.1016/j.orhc.2021.100290
7. Pirabán A, Guerrero WJ, Labadie N. Survey on blood supply chain management: models and methods. Comput Oper Res. 2019;112:104756. https://doi.org/10.1016/j.cor.2019.07.014
8. Zahiri B, Pishvaee MS. Blood supply chain network design considering blood group compatibility under uncertainty. Int J Prod Res. 2017;55(7):2013–33. https://doi.org/10.1080/00207543.2016.1262563
9. Canadian Blood Services. Inventory planning and management. Inventory best practices. doi:https://doi.org/10.1002/9781119203087.ch8
10. Stanger SHW, Yates N, Wilding R, Cotton S. Blood inventory management: hospital best practice. Transfus Med Rev. 2012;26(2):153–63. https://doi.org/10.1016/j.tmrv.2011.09.001
11. Jacka M, Nahirniak S. In critically ill adults, transfusion of fresh vs standard-issue red blood cells did not differ for 90-day mortality. Ann Intern Med. 2015;163(2):JC5. https://doi.org/10.7326/ACPJC-2015-163-2-005
12. Keir AK, Wilkinson D, Andersen C, Stark MJ. Washed versus unwashed red blood cells for transfusion for the prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2015;2015(1):91. https://doi.org/10.1002/14651858.CD011484
13. Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. N Engl J Med. 2016;375(20):1937–45. https://doi.org/10.1056/nejmoa1609014
14. Webert KE, Cook RJ, Couban S, Carruthers J, Lee KA, Blajchman MA, et al. A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. Transfusion. 2008;48(1):81–91. https://doi.org/10.1111/j.1537-2995.2007.01485.x
15. Sensebé L, Giraudeau B, Bardiaux L, Deconinck E, Schmidt A, Bidet M-L, et al. The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: results of a prospective, randomized, open, blinded end point (PROBE) study. Blood. 2005;105(2):862–4. https://doi.org/10.1182/blood-2004-05-1841
16. Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;2021(5):CD013600. https://doi.org/10.1002/14651858.CD013600.pub4
17. Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021;27:2012–24. https://doi.org/10.1038/s41591-021-01488-2
18. Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM, et al. Severe acute respiratory syndrome coronavirus 2 convalescent plasma versus standard plasma in coronavirus disease 2019 infected hospitalized patients in New York: a double-blind randomized trial. Crit Care Med. 2021;49(7):1015–25. https://doi.org/10.1097/CCM.0000000000005066
19. Diago-Sempere E, Bueno JL, Sancho-López A, Rubio EM, Torres F, de Molina RM, et al. Evaluation of convalescent plasma versus standard of care for the treatment of COVID-19 in hospitalized patients: study protocol for a phase 2 randomized, open-label, controlled, multicenter trial. Trials. 2021;22(1):70. https://doi.org/10.1186/s13063-020-05011-9
20. AlQahtani M, Abdulrahman A, Almadani A, Alali SY, al Zamrooni AM, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. Sci Rep. 2021;11(1):9927. https://doi.org/10.1038/s41598-021-89444-5
21. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind

controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021;131(13):e150646. https://doi.org/10.1172/JCI150646
22. Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, et al. Randomized controlled trial of early outpatient COVID-19 treatment with high-titer convalescent plasma. medRxiv Prepr Serv Health Sci. 2021. https://doi.org/10.1101/2021.12.10.21267485
23. Masser BM, Ferguson E, Thorpe R, Lawrence C, Davison TE, Hoad V, et al. Motivators of and barriers to becoming a COVID-19 convalescent plasma donor: a survey study. Transfus Med. 2021;31(3):176–85. https://doi.org/10.1111/tme.12753
24. NCT04348656. CONvalescent plasma for hospitalized adults with COVID-19 respiratory illness (CONCOR-1). https://clinicaltrials.gov/show/NCT04348656. 2020. https://doi.org/10.1002/central/CN-02091713/full
25. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The remap-cap (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study rationale and design. Ann Am Thorac Soc. 2020;17(7):879–91. https://doi.org/10.1513/AnnalsATS.202003-192SD
26. NCT04377568. Efficacy of human coronavirus-immune convalescent plasma for the treatment of COVID-19 disease in hospitalized children. https://clinicaltrials.gov/show/NCT04377568. 2020.
27. Abdinnour-Helm S. Network design in supply chain management. Int J Agil Manag Syst. 1999;1(2):99–106. https://doi.org/10.1108/14654659910280929
28. Calabrò RS, Manuli A, De Cola MC, Bramanti P. Innovation technology in neurorehabilitation: introducing a hub and spoke model to avoid patient "migration" in Sicily. J Health Organ Manag. 2020;34(2):207–14. https://doi.org/10.1108/JHOM-07-2019-0200
29. Elrod JK, Fortenberry JL. The hub-and-spoke organization design: an avenue for serving patients well. BMC Health Serv Res. 2017;17:457. https://doi.org/10.1186/s12913-017-2341-x
30. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208
31. CONCOR-1. Checking product inventory, reserving a unit, assigning a unit, and freeing a unit in REDCap. YouTube; 2020 https://www.youtube.com/watch?v=LIcWw6b0ylQ&ab_channel=CONCOR-1
32. Cooper I, Mondal A, Antonopoulos CG. A SIR model assumption for the spread of COVID-19 in different communities. Chaos Solitons Fract. 2020;139:110057. https://doi.org/10.1016/j.chaos.2020.110057
33. Weissman GE, Crane-Droesch A, Chivers C, Luong TB, Hanish A, Levy MZ, et al. Locally informed simulation to predict hospital capacity needs during the COVID-19 pandemic. Ann Intern Med. 2020;173(1):21–8. https://doi.org/10.7326/M20-1260
34. Akbari-Moghaddam M, Li N, Down DG, Arnold DM, Callum J, Bégin P, et al. Data-driven fair resource allocation for novel emerging epidemics: a COVID-19 convalescent plasma case study. arXiv. 2021;1–19. https://arxiv.org/abs/2106.14667
35. Friedman JH. Multivariate adaptive regression splines. The Annals of Statistics. 1991;19(1):1–67. https://doi.org/10.1214/aos/1176347963
36. Jarrett JE, Khumuwala SB. A study of forecast error and covariant time series to improve forecasting for financial decision making. Manag Financ. 1987;13(2):20–4. https://doi.org/10.1108/eb013583
37. Lu M, Chen Y. Improved estimation and forecasting through residual-based model error quantification. SPE Journal. 2020;25:951–68. doi:10.2118/199358-PA
38. Carpenter C. Model error estimation improves forecasting. J Petrol Tech. 2020;72(04):67–8. https://doi.org/10.2118/0420-0067-jpt
39. Ajmani PS. Blood group and immunology. In: *Immunohematology and blood banking*. Springer, Singapore. 2020;7–23. https://doi.org/10.1007/978-981-15-8435-0_2
40. Van Rossum G, Drake FL. Python 3 reference manual. *CreateSpace*. Scotts Valley, CA. 2009.
41. Canadian Blood Services. Blood types. Canadian Blood Services, Ottawa Ontario, Canada. 2014. Accessed May 22, 2022. https://www.blood.ca/en/blood/donating-blood/blood-types
42. Mansournia MA, Higgins JPT, Sterne JAC, Hernán MA. Biases in randomized trials. Epidemiology. 2017;28(1):54–9. https://doi.org/10.1097/EDE.0000000000000564
43. Chowdhury MEH, Rahman T, Khandakar A, Khandakar A, Al-Madeed S, Zughaier SM, et al. An early warning tool for predicting mortality risk of COVID-19 patients using machine learning. *Cognit Comput*. 2021;1–16.
44. Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A tool for early prediction of severe coronavirus disease 2019 (covid-19): a multicenter study using the risk nomogram in Wuhan and Guangdong, China. Clin Infect Dis. 2020;71(15):833–40. https://doi.org/10.1093/cid/ciaa443
45. Tomar A, Gupta N. Prediction for the spread of COVID-19 in India and effectiveness of preventive measures. Sci Total Environ. 2020;728:138762. https://doi.org/10.1016/j.scitotenv.2020.138762
46. Khajanchi S, Sarkar K. Forecasting the daily and cumulative number of cases for the COVID-19 pandemic in India. Chaos. 2020;30(7):071101. https://doi.org/10.1063/5.0016240
47. Baron AF, Boulant O, Panico I, Vayatis N. A compartmental epidemiological model applied to the covid-19 epidemic. Image Process Line. 2021;11:105–19. https://doi.org/10.5201/IPOL.2021.323
48. Mwalili S, Kimathi M, Ojiambo V, Gathungu D, Mbogo R. SEIR model for COVID-19 dynamics incorporating the environment and social distancing. BMC Res Notes. 2020;13(1):352. https://doi.org/10.1186/s13104-020-05192-1
49. Silal SP, Little F, Barnes KI, White LJ. Sensitivity to model structure: a comparison of compartmental models in epidemiology. Health Syst. 2016;5(3):178–91. https://doi.org/10.1057/hs.2015.2
50. Nikolopoulos K, Punia S, Schäfers A, Tsinopoulos C, Vasilakis C. Forecasting and planning during a pandemic: COVID-19 growth rates, supply chain disruptions, and governmental decisions. Eur J Oper Res. 2021;290(1):99–115. https://doi.org/10.1016/j.ejor.2020.08.001
51. Ferstad JO, Gu A, Lee RY, Thapa I, Shin AY, Salomon JA, et al. A model to forecast regional demand for COVID-19 related hospital beds. medRxiv. 2020.

52. Box GEP, Tiao GC. Intervention analysis with applications to economic and environmental problems. J Am Stat Assoc. 1975; 70(349):70–9. https://doi.org/10.1080/01621459.1975.10480264
53. Lin HH, Beck CL, Bloom MJ. On the use of multivariable piecewise-linear models for predicting human response to anesthesia. IEEE Trans Biomed Eng. 2004;51(11):1876–87. https://doi.org/10.1109/TBME.2004.831541
54. Brito BH, Finardi EC, Takigawa FYK. Mixed-integer nonseparable piecewise linear models for the hydropower production function in the unit commitment problem. Electr Power Syst Res. 2020;182:106234. https://doi.org/10.1016/j.epsr.2020.106234
55. Bekker R, uit het Broek M, Koole G. Modeling COVID-19 hospital admissions and occupancy in The Netherlands. Eur J Oper Res. 2023;304(1):207–18. https://doi.org/10.1016/j.ejor.2021.12.044
56. Segev R. Well-being and fairness in the distribution of scarce health resources. J Med Philos. 2005;30(3):231–60. https://doi.org/10.1080/03605310590960120
57. Pu L. Fairness of the Distribution of Public Medical and Health Resources. Front Public Health. 2021;9:768728. https://doi.org/10.3389/fpubh.2021.768728
58. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med. 2020;382(21):2049–55. https://doi.org/10.1056/nejmsb2005114

SUPPORTING INFORMATION

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How to cite this article: Li N, Zeller MP, Shih AW, Heddle NM, St. John M, Bégin P, et al. A data-informed system to manage scarce blood product allocation in a randomized controlled trial of convalescent plasma. Transfusion. 2022;62(12): 2525–38. https://doi.org/10.1111/trf.17151