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Transfusion Practices in 12 Neonatal Networks: Are We Closer to Adopting a Restrictive Transfusion Approach?

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Keywords
Blood transfusions · Transfusion policy · Extremely preterm infants

Abstract
Introduction: Recent evidence suggests a restrictive approach toward blood transfusions for management of preterm infants. Objective was to survey blood transfusion practises in preterm neonates <29 weeks' gestation among 12 population-based neonatal networks participating in the International Network for Evaluating Outcomes in Neonates

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(iNeo). ***Methods:*** An online survey based on 2023 practices was sent to 608 neonatal intensive care units (NICUs): Australia/New Zealand (30), Brazil (20), Canada (32), Finland (5), France (70), Israel (26), Japan (292), Poland (56), Spain (55), Sweden (9), Switzerland (9), and Tuscany, Italy (4). Transfusion thresholds in 4 different scenarios were surveyed: (a) infants invasively ventilated within first 7 postnatal days, (b) infants invasively ventilated after 7 days, (c) stable infants on noninvasive respiratory support, and (d) stable infants requiring no respiratory support. ***Results:*** A total of 382 NICUs (63%) responded. Transfusion practices varied within networks and between countries. For invasively ventilated infants, the transfusion threshold during first 7 days after birth was a hematocrit ≤35% in 79% of NICUs, and at an age ≥8 days, the transfusion threshold was a hematocrit ≤30% in 68% of NICUs. For stable infants on noninvasive ventilation, the transfusion threshold was a hematocrit ≤30% in 80%, and in those without respiratory support, the transfusion threshold was a hematocrit of ≤25% in 68% of NICUs. ***Conclusions:*** Variations exist in blood transfusion practises between countries and within networks. A restrictive transfusion approach based on recent recommendations has been adopted by more than two-thirds of NICUs. Additional research is needed to evaluate whether practices align with intentions and how they impact outcomes.

Introduction

Blood transfusions are commonly administered in neonatal intensive care units (NICUs), with 90% of extremely low birth weight (ELBW) infants receiving a red blood cell transfusion (RBCT) at least once during their hospital stay [1]. Previous randomized trials have not shown any significant differences between a lower or higher hemoglobin threshold for RBCT when it comes to short-term neonatal outcomes [2, 3]. However, a lack of long-term outcome data has been an obstacle in changing practice from a liberal to a restrictive RBCT policy. Recently, two large randomized controlled trials, the Effects of Liberal vs. Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants (ETTNO trial) [4] and the Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants (TOP trial) [5], reported the neurocognitive outcomes of ELBW infants exposed to RBCT. Both studies showed that a lower vs. higher RBCT threshold was not associated with adverse neurocognitive outcomes. Consequently, a more restrictive approach for RBCT has been recommended [6–8].

Most countries do not have national guidelines for neonatal transfusions. Thus, adoption of a restrictive RBCT approach is not policy-driven and is generally physician-dependent. There are limited recent data on transfusion practices in preterm infants. An international survey of transfusion practices for ELBW infants, based predominantly on responses from neonatologists practising in the USA, reported that about half of the participating NICUs did not have unit guidelines and RBCTs were strongly influenced by simultaneous receipt of respiratory support [9]. This survey showed a wide variation in transfusion hemoglobin thresholds, regardless of postnatal age. Patel et al. [10], in a retrospective cohort study, also found wide variability in pre-transfusion hemoglobin levels and concluded that a large proportion of neonatal transfusions are administered at higher hemoglobin thresholds compared to those supported by the best evidence. Our aim was to survey blood transfusion practises in extremely preterm neonates of <29 weeks' gestation among neonatal units of 12 population-based neonatal networks and to assess the adoption of a restrictive transfusion policy.

Methods

This was an observational study that used a pre-piloted online questionnaire to assess transfusion practices. The survey included items on multiple aspects of neonatal care subjects including infrastructure, staffing, and neonatal practices. The survey was sent to collaborators of the International Network for Evaluating Outcomes of Neonates (iNeo). The iNeo is a large international collaboration created to improve patient-oriented outcomes for preterm infants by comparing outcomes at the country, regional, or unit level [11, 12]. The study was approved by the Research Ethics Board of Mount Sinai Hospital, Toronto, and by the directors of the iNeo collaboration.

The questionnaire was sent to the directors or representatives of 608 NICUs participating in iNeo in Australia/New Zealand (ANZNN, n = 30), Brazil (BNN, n = 20), Canada (CNN, n = 32), Finland (FinMBR, n = 5), France (SFN, n = 70), Israel (INN, n = 26), Japan (NRNJ, n = 292), Poland (PNN, n = 56), Spain (SEN1500, n = 55), Sweden (SNQ, n = 9), Switzerland (SNN, n = 9), and Tuscany, Italy (TuscanNN, n = 4). The responses were based on practices in 2023. Two reminders were sent. The responses were recorded anonymously as the code for each individual site was distributed by the Network Directors who received them from the iNeo informatics manager.

A section of the questionnaire evaluated transfusion practices. Four different scenarios were provided to assess how postnatal age and type of respiratory support influenced the unit policy of hematocrit thresholds applied for blood transfusion. For each clinical scenario, the responders were requested to choose the hematocrit threshold that represented their NICU practice in general in the absence of any other ongoing hematological or hemodynamic issue with the neonate: 25%, 30%, 35%, 40%, above 40%, no threshold, or physician-dependent\unknown. Situations included (a) infants invasively ventilated within first 7 postnatal days, (b) infants invasively ventilated after 7 postnatal days, (c) stable infants on noninvasive respiratory support, and (d) stable infants requiring no respiratory support. The definition of restrictive or liberal RBCT policy was based on previous studies [4, 5]. Restrictive hematocrit thresholds for transfusions for each scenario were considered: a – 35%, b – 30%, c – 30%, d – 25%. The survey also asked if unit transfusion guidelines existed.

The number and percent of NICUs using each RBCT threshold was calculated for each participating network and for the iNeo cohort of preterm infants <29 weeks' gestation. The approaches to each clinical scenario were assessed and graphically displayed using the hematocrit transfusion threshold reported [4].

Results

The survey was sent to 608 NICU directors or representatives collaborating with iNeo. The response rate was 382/608 units (63%) and varied from 37% to 100% among participating networks. The number of responding units in each neonatal network varied between 4 (Tuscany, Italy) and 108 (Japan). The annual median number of admissions per network ranged from 268 (Tuscany, Italy) and 1000 (Australia-New Zealand).

Transfusion guidelines were present in 283 of 382 NICUs (74%; intercountry variation 48%–100%). Transfusion practices varied both within networks and between countries (Table 1). In neonates receiving invasive ventilation in first 7 postnatal days, 50% (intercountry variation 25–89%) of units responded administration of transfusion when hematocrit was ≤35%, whereas 29% (intercountry variation 11–75%) of units responded administration of transfusion when hematocrit was ≤30%.

In neonates receiving invasive ventilation after first 7 postnatal days, 16% (intercountry variation 0–40%) of units responded administration of transfusion when hematocrit is ≤35%, whereas 68% (intercountry variation 41–89%) of units responded administration of transfusion when hematocrit is ≤30%. In stable neonates receiving noninvasive respiratory support, 28% (intercountry variation 0–78%) of units responded administration of transfusion when hematocrit is ≤30%, whereas 52% (intercountry variation 20–100%) of units responded administration of transfusion when hematocrit is ≤25%.

In neonates not on any respiratory support, 68% (intercountry variation 47–100%) of units responded transfusion when hematocrit is ≤25%, whereas most other units responded no threshold or physician-dependent decision to transfuse. For infants requiring invasive respiratory support 95–98% of NICUs had a predefined hematocrit threshold for RBCT; however, for stable infants with or without noninvasive respiratory support, only 88%–89% of NICUs had a known threshold.

We also assessed respondent's practice in alignment with a restrictive RBCT threshold with each scenario (Fig. 1). The majority of NICUs (68–80%) were within what could be considered restrictive RBCT policy. A liberal RBCT threshold was more commonly used (21%) in invasively ventilated infants older than 7 days.

Discussion

In this international survey of transfusion practices of NICUs participating in the iNeo collaboration, we identified variations in transfusion practices both within and between networks. Although variations exist, 68%–80% of NICUs reported RBCT hematocrit thresholds which were compatible with a restrictive transfusion policy.

Use of RBCT in ELBW infants is common practice. RBCT administration is generally dependent on the infants' hemodynamic stability and respiratory status. For unstable invasively ventilated infants, the rationale for a higher RBCT threshold is to increase the oxygen carrying capacity [13] by maintaining a higher hematocrit. For hemodynamically stable infants, the transfusion threshold has been influenced by the possible detrimental effect of iron deficiency on the developing brain [14]; however, iron deficiency is not synonymous with anemia of prematurity, especially in infants that have received RBCTs. The number of RBCTs that ELBW infants receive can be decreased by decreasing the transfusion threshold. Many countries do not have

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Table 1. Transfusion thresholds in various clinical scenarios by neonatal network[a]

Networks	ANZNN (Australia-New Zealand	BNN (Brazil)	CNN (Canada)	FinMBR (Finland)	SFN (France)	INN (Israel)	NRNJ (Japan)	PNN (Poland)	SEN1500 (Spain)	SNN (Swiss)	SNQ (Sweden)	TuscanNN (Tuscany)	All
Number of units	21	20	30	5	68	23	108	55	30	9	9	4	382
Response rate, %	70	100	94	100	97	92	37	98	55	100	100	100	63
Invasively ventilated first 7 postnatal days													
Hematocrit ≤25%	1 (5)	1 (5)			1 (1.5)		4 (4)	1 (2)	2 (7)				10 (3)
Hematocrit ≤30%	5 (24)	10 (50)	4 (13)	1 (20)	23 (34)	3 (13)	31 (28)	12 (22)	8 (27)	1 (11)		3 (75)	101 (26)
Hematocrit ≤35%	9 (43)	7 (35)	16 (53)	4 (80)	37 (55)	11 (48)	46 (42)	26 (47)	17 (57)	8 (89)	8 (89)	1 (25)	190 (50)
Hematocrit ≤40%	3 (14)		2 (7)		2 (3)	9 (39)	5 (5)	7 (13)	1 (3)		1 (11)		30 (8)
Hematocrit >40%			1 (3)				3 (3)	6 (11)					10 (3)
No threshold, %		1 (5)					5 (5)		1 (3)				7 (2)
Physician-dependent/ unknown, %	3 (14)	1 (5)	7 (24)		5 (7)		14 (13)	3 (5)	1 (3)				34 (9)
Invasively ventilated , postnatal age ≥8 days													
Hematocrit ≤25%	1 (5)	5 (25)	2 (7)		7 (11)		13 (12)	6 (11)	4 (13)	1 (11)		1 (25)	40 (10)
Hematocrit ≤30%	13 (62)	10 (50)	17 (56)	3 (60)	51 (75)	14 (61)	45 (41)	33 (60)	17 (57)	7 (78)	8 (89)	3 (75)	221 (58)
Hematocrit ≤35%	3 (14)	3 (15)	4 (13)	2 (40)	5 (7)	7 (30)	23 (21)	6 (11)	6 (20)	1 (11)	1 (11)		61 (16)
Hematocrit ≤40%						2 (9)	5 (5)	7 (13)					14 (4)
Hematocrit >40%							3 (3)						3 (1)
No threshold, %		1 (5)					5 (5)		1 (3)				7 (2)
Physician-dependent/ unknown, %	4 (19)	1 (5)	7 (24)		5 (7)		14 (13)	3 (5)	2 (7)				36 (9)
Stable, receiving noninvasive respiratory support													
Hematocrit ≤25%	13 (61)	11 (55)	11 (37)	1 (20)	47 (69)	10 (43)	52 (48)	22 (40)	18 (60)	7 (78)	2 (22)	4 (100)	198 (52)
Hematocrit ≤30%	3 (14)	5 (25)	9 (30)	3 (60)	14 (20.5)	8 (35)	22 (20)	26 (47)	6 (20)	2 (22)	7 (78)		105 (28)
Hematocrit ≤35%	2 (10)		1 (3)		1 (1.5)	2 (9)	4 (4)	2 (4)	1 (3)				13 (3)
Hematocrit ≤40%							2 (2)						2 (0.5)
Hematocrit >40%							1 (2)						1 (0.3)
No threshold, %	1 (5)	3 (15)			2 (3)	2 (9)	9 (8)	1 (2)	2 (7)				20 (5)
Physician-dependent/ unknown, %	2 (10)	1 (5)	9 (30)	1 (20)	4 (6)	1 (4)	18 (16)	4 (7)	3 (10)				43 (11.2)
Stable, receiving no respiratory support													
Hematocrit ≤25%	15 (70)	13 (65)	14 (47)	4 (80)	54 (79)	20 (87)	62 (57)	41 (75)	18 (60)	9 (100)	6 (67)	3 (75)	259 (68)
Hematocrit ≤30%	2 (10)				1 (1.5)		8 (7)	2 (4)	1 (3)		3 (33)		17 (5)
Hematocrit ≤35%					1 (1.5)		2 (2)						3 (1)
Hematocrit ≤40%							1 (1)						1 (0.3)

Table 1 (continued)

Networks	ANZNN (Australia-New Zealand	BNN (Brazil)	CNN (Canada)	FinMBR (Finland)	SFN (France)	INN (Israel)	NRNJ (Japan)	PNN (Poland)	SEN1500 (Spain)	SNN (Swiss)	SNQ (Sweden)	TuscanNN (Tuscany)	All
Hematocrit >40%							1 (1)						1 (0.3)
No threshold, %	2 (10)	5 (25)	1 (3)	1 (20)	6 (9)	3 (13)	15 (14)	4 (7)	8 (27)			1 (25)	46 (12)
Physician-dependent/ unknown, %	2 (10)	2 (10)	15 (50)		6 (9)		19 (18)	8 (14)	3 (10)				55 (14.4)

[a]Neonatal networks: ANZNN, Australian and New Zealand Neonatal Network; BNN, Brazil Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; SFN, Société Française de Néonatalogie; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; PNN, Polish Neonatal Network; SEN1500, Spanish Neonatal Network; SNN, Swiss Neonatal Network; SNQ, Swedish Neonatal Quality Register; TuscanNN, Tuscany Neonatal Network.

transfusions guidelines; thus, the thresholds for transfusion are determined by each NICU or even individual health care teams. Nevertheless, a restrictive RBCT threshold was adopted by many NICUs following the publication of two major trials, the ETTNO [4] and the TOP trials [5], reporting an absence of long-term adverse effects of a restrictive RBCT.

RBCTs are essential and lifesaving in unstable or severely anemic infants; however, there are known risks of RBCTs such as transfusion-associated gut injury, transfusion-associated cardiac overload, and mortality [15, 16]. In preterm infants, multiple blood transfusions may worsen conditions associated with inflammation, such as bronchopulmonary dysplasia and retinopathy of prematurity [15], thus decreasing RBCT use is an obvious goal. Decreasing RBCTs in the NICU by applying lower transfusion thresholds is one of a number of methods that may be employed to obtain this goal. Delayed cord clamping achieves a higher initial hemoglobin and is common neonatal practice which has shown in systematic reviews to reduce receipt of RBCT. Use of cord blood transfusions [17] increases hemoglobin without depleting fetal hemoglobin and may also be beneficial due to presence of mesenchymal stem cells that are considered protective against several prematurity associated complications [18]. Improving phlebotomy losses [1], which is a major cause of anemia of prematurity, should be part of standard practice. Prevention of anemia of prematurity by use of erythropoiesis stimulating agents such as erythropoietin or darbepoetin is known to decrease or prevent RBCT need in ELBW infants [15].

A meta-analysis of 12 trials, including a total of 4,380 infants, compared restrictive vs. liberal transfusion thresholds in anemic preterm infants [19]. Infants' age at first transfusion in the restrictive transfusion group was higher than that of the liberal group ($p = 0.004$). However, restrictive transfusion was associated with more time on supplemental oxygen ($p < 0.001$) and ventilator or continuous positive airway pressure ($p = 0.001$). For all other outcomes, the two transfusion strategies were comparable. While both transfusion strategies were found to be effective and safe in preterm infants, the liberal strategy shortened the length of respiratory support, the significance of which on long-term respiratory and neurodevelopmental outcome is to be elucidated.

Temporal changes in RBCTs were evaluated in Canada by Kier et al. [20] and reported a trend towards fewer RBCT was seen for preterm infants born at 26–29 weeks' gestation; however, for preterm infants born at 23–25

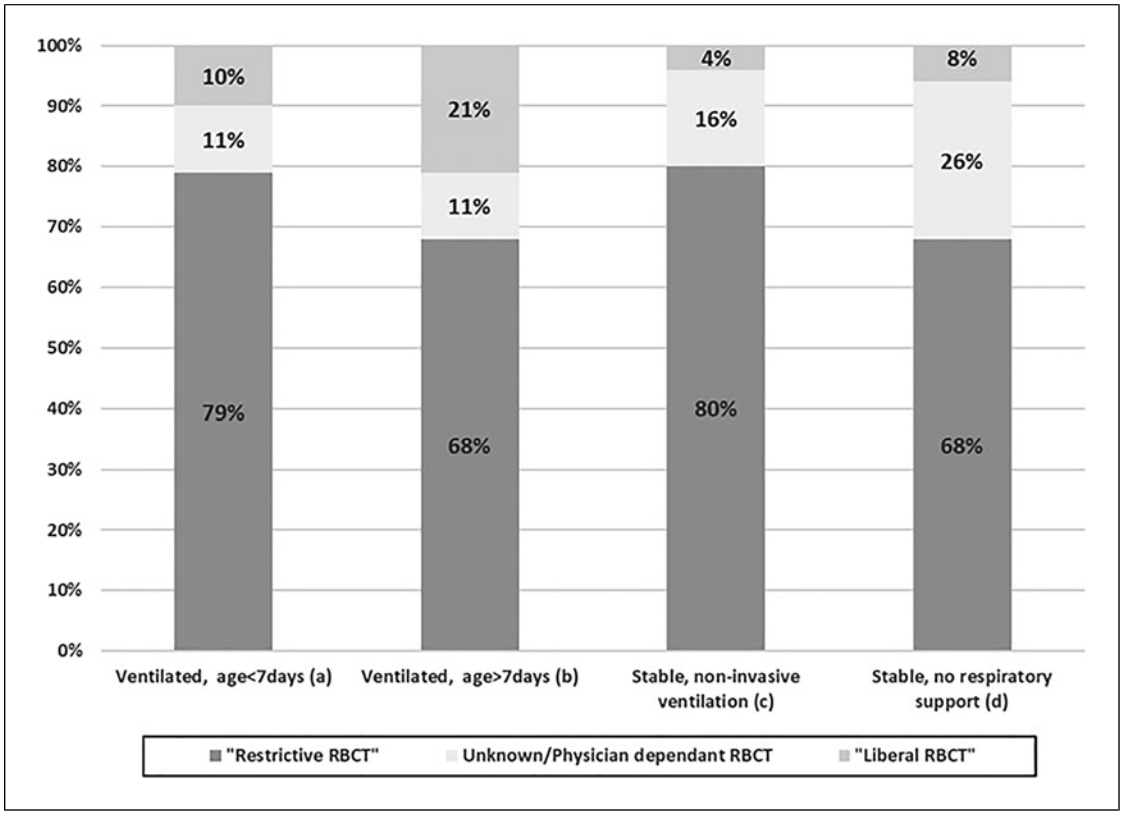

Fig. 1. Restrictive vs. liberal RBCT threshold in the iNeo networks. Restrictive hematocrit thresholds for transfusions were considered: a – 35%, b – 30%, c – 30%, d – 25%. RBCT, red blood cell transfusion.

weeks' gestation, RBCT remained unchanged or increased. In a European survey of transfusion practices performed before publication of the ETTNO and TOP studies, 70% of NICUs transfused at thresholds above a restrictive threshold and 22% of NICUs below restrictive thresholds [21]. Houben et al. [22] in a recent European study, evaluated the implementation of restrictive RBCT thresholds. The study identified wide variations in transfusion practices between countries. Compared to the ETTNO and TOP trials, a restrictive transfusion threshold was used in 36.4%–44.4% of transfusions. Heeger et al. [23] in a recent study from the Netherlands found that 47% of RBCTs were administered above recommended threshold. Mo et al. [24] studied transfusion practises in preterm infants <32 weeks' gestation based on the Chinese Neonatal Network in a retrospective study. Of the RBCTs, 25.6% were administered to infants on invasive respiratory support, 51.3% to infants on noninvasive respiratory support, and 23.1% to infants without respiratory support. An increased rate of necrotizing enterocolitis ($p = 0.001$) and a longer hospital stay ($p < 0.001$) were shown for infants receiving RBCT above the recommended threshold. This study highlights the dilemma among infants on noninvasive respiratory support who are often stable; however, they may represent the largest group to whom RBCTs are administered.

Our study surveyed the RBCT threshold use when a restrictive RBCT threshold policy was well established. When planning the survey, the representatives of the participating iNeo countries agreed to use hematocrit rather than hemoglobin thresholds as this was commonly used for RBCT decisions. The survey did not specify if the hematocrit values were venous or capillary; thus, the units responded according to their standard practice. Neonatal conditions such as cardiovascular instability or sepsis, for which a higher transfusion threshold is often practiced, were not surveyed as part of this project. We surveyed 4 common clinical scenarios. Variation in transfusion thresholds was seen within each network; however, 68%–80% of NICU responded that they employed a restrictive RBCT policy. Finland, Switzerland, Sweden, and Tuscany had a more uniform unit RBCT policy compared to other networks, in particular regarding invasively ventilated infants. In comparison to previous reports [20–23], a

restrictive RBCT approach appears to be more commonly used. Nearly all NICUs employed predefined transfusion thresholds. For infants requiring respiratory support, only 2–5% of NICUs did not have a transfusion threshold. For stable non-ventilated infants, it is more difficult to determine a transfusion threshold, as evident by the higher number of NICUs (26%) that did not have a transfusion threshold or in which transfusions were physician dependent.

We undertook a large international survey on transfusion practices and obtained a good response rate; however, 37% of NICUs did not respond and their policies may differ from those of responders. The present survey sought to study practices in preterm infants at risk for RBCTs. We chose to focus on the preterm infant population <29 weeks' gestation, which includes nearly all ELBW infants and also includes many very low birth weight infants (<1,500 g). Thus, the survey is more representative of the majority of preterm population requiring RBCTs compared to the ELBW cohort included in the trials [4, 5]. The definition of a restrictive transfusion policy for all scenarios surveyed was chosen as that similar to previously studies [4, 5]. For stable infants, the lowest hematocrit threshold of 25% may not be of sufficient resolution, as for these infants a RCBT threshold of 21–22% may be more appropriate as also suggested in guideline for critically ill children. [4, 5, 25]. The scenarios are encountered in every NICU and represent common clinical dilemmas. A limitation of this study is that it is based on a survey and not actual practice as to what happens in real-world situations. It will be useful and important to follow this survey with practices and their association with outcomes of neonates.

In conclusion, variations exist in blood transfusion practises of very preterm infants between countries and within networks. Despite the observed variation, a restrictive transfusion threshold was applied by more than two thirds of participating NICUs. Additional research is needed to evaluate whether practices align with intentions and how they impact outcomes. Complete list of iNeo investigators is in Supplementary material (for all online suppl. material, see https://doi.org/10.1159/000546612).

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Statement of Ethics

Data collection and data transfer from individual networks were approved by the Research Ethics Boards of the participating networks in the respective countries and by the iNeo Steering Committee. Specific ethics approval for this project was obtained from the Mount Sinai Hospital Research Ethics Board and the iNeo Steering Committee. This study protocol was reviewed and approved by Research Ethics Board (MSH REB#12-0336-E). Informed consent from individual patients was waived due to retrospective nature of this database study.

Conflict of Interest Statement

Prof. Maximo Vento and Dr. Tetsuya Isayama were both a member of the journal's Editorial Board at the time of submission. Other authors have no conflicts of interest to declare.

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Author Contributions

Drs. Gil Klinger and Prakesh S. Shah were involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and revising it critically for important intellectual content. Neha Goswami performed the statistical analyses and was involved in the conception and design of the study, interpretation of results, and critically revising the article for important intellectual content. Kjell Helenius, Max Vento, Satoshi Kusuda, Mikael Norman, Renato Soibelman Procianoy, Valerie Biran, Dirk Bassler, Brian Reichman, Aleksandra Skubisz, Malcolm Battin, Liisa Lehtonen, Kei Lui, Annalisa Mori, Marc Beltempo, Mark Adams, Laura San Feliciano, and Tetsuya Isayama were involved in the conception and design of the study, interpretation of results, and critically revising the article for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Prakesh S. Shah, Mount Sinai Hospital, Toronto, ON, Canada, has full access to the data. He takes responsibility for the integrity of the data and the accuracy of the data analysis. The data analyses were conducted by Neha Goswami. Data are confidential and not available for public access. Further inquiries can be directed to the corresponding author.

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