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Real-World Safety Data From the World Apheresis Association Registry for the Spectra Optia Apheresis System

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ABSTRACT

In this study we analyzed 12 years of adverse events, (AE) data from the World Apheresis Association, (WAA) Registry specific to the Spectra Optia Apheresis System. We queried WAA Registry data, (2012–2023) on apheresis procedures performed exclusively on the Spectra Optia Apheresis System. We categorized AEs by severity, (mild, moderate, and severe), and ordered them by year. We then analyzed and presented AEs associated with the following variables: diagnosis, procedure type, vascular access, and replacement fluid type, and causes of procedural interruption. We identified 51 567 apheresis procedures specific to the Spectra Optia Apheresis System within the data set. AE rates from 2012 to 2023 for mild, moderate, and severe were 1.43%, 2.81%, and 0.21%, respectively. Procedures associated with the lowest AE rates include red blood cell exchange and therapeutic plasma exchange. The most common mild and moderate AEs include tingling and hypotension and AEs related to vascular access. The highest rates of mild and moderate AEs were associated with cellular collections. The highest rate of severe AEs was associated with the use of 3.5% albumin as replacement fluid. Other variables impacting patient safety are identified. AE rates could not be compared to the median length of procedure since this time variable is not currently collected in the Registry. This is the first device-specific analysis of the WAA Registry data, bringing prior safety reporting into even sharper focus. Device-specific safety analysis like this will help practitioners better understand potential safety concerns associated with a commonly used apheresis device, including various separation modalities and accessories, thus supporting improved procedure management.

Research and writing were performed at both Terumo BCT, Inc. and at Umea University.

1 | Introduction/Background

Therapeutic apheresis (TA), is prescribed to patients as a first- or second-line therapy for up to 45 listed diseases and conditions according to the American Society for Apheresis (ASFA) most recent 2023 guidance [1]. TA is frequently utilized in the chronic management of numerous diseases and may also be used when drug therapy fails or in cases of life-threatening emergencies.

Fully automated apheresis devices became available in the 1970s and have been used routinely in patient care since the 1980s [2]. For many years now, apheresis researchers have carefully monitored the rate and type of procedure-related adverse events [3, 4]. However, with an ever-expanding list of diseases being treated, changes to the sites of service, demographic changes among patient populations, and with a constantly evolving list of concomitant drug therapies, it is important to continuously monitor procedural safety to ensure best clinical practices are updated accordingly. For this purpose, the field requires consistent reporting and reliable sources of safety and performance data.

While apheresis-related adverse events have been reported previously, most are from single sites of care or are limited in the variety of apheresis protocols examined [5–8]. More comprehensive analyses draw from a large pool of patient data and cover a wide variety of apheresis procedures [9]. The best data, however, cover many sites of care and include the largest pool of procedural data available. Toward this goal, several prominent groups maintain large and active registries and have reported adverse events to varying degrees. These include the American Society for Apheresis (ASFA) Disease registry [10], the Globin Regional Data and Discovery, (GRnDAD) registry [11], and the World Apheresis Association (WAA)- World Apheresis Registry [12].

The WAA Registry was established and launched in December 2002 as an internet registry based on the concepts of the Canadian, French and Swedish registries. The registry allows any center worldwide to participate with data input without cost to the center. Each center can download its own data at any time, such as for its own reports. After informed consent is achieved from the patient, entry of the data can be done at the bedside or later. Analyses of data are performed intermittently after merging the information from the different centers regarding entered information such as safety issues, time trends, effect variables of diagnoses, procedures used, and outcome variables. Publications from the WAA Registry have provided thorough and comprehensive reviews of data from various apheresis procedures. These findings have reported that apheresis procedures are generally safe, with a low total adverse event (AE) rate, (~3%), where severe AE rates were the lowest at 0.1%–0.15% [13, 14]. While this is reassuring for patients, caregivers, prescribers, and other apheresis stakeholders, important safety information remains hidden when data remain aggregated from multiple apheresis devices. The reporting of only aggregated data may limit the utility of the safety information, as many critical developments around apheresis care can be device specific.

The purpose of the current analysis is to obtain important safety data specific to the Spectra Optia, a widely used continuous-flow, centrifuge-based apheresis system manufactured by Terumo Blood and Cell Technologies Inc. (Lakewood, CO). While safety data for apheresis procedures performed using the Spectra Optia have been reported previously, the size of the data pools was limiting, especially when trying to quantify the real-world risk of very rare serious adverse events that can occur at rates of $<0.1\%$. With this in mind, we disaggregated recent data from the WAA Registry, reporting only on therapeutic apheresis procedures performed using the Spectra Optia to better define potential device-specific safety considerations.

2 | Materials and Methods

2.1 | Registry

The World Apheresis Association, (WAA) is an umbrella organization of international professional societies that is devoted to the scientific, medical, administrative and educational aspects of apheresis. Among other important contributions to the field, the WAA maintains a comprehensive clinical registry [13]. Data entry by facility type includes academic centers ($n=32$, 74.4%), county hospitals ($n=5$, 11.6%), national providers ($n=4$, 9.3%), and private units ($n=2$, 4.7%). Registration is performed consecutively as confirmed by the registry users. The WAA registry data is maintained and was accessed in a manner as described previously [14]. Data is entered at the local center level. The data are checked for completeness and continuously cleaned for significant outliers or implausible data by the registry holder. The registry data is audited with a validity check randomized for two periods (2015 and 2023). At least 500 consecutive procedures were calculated each period (total of 1558). Sixteen procedures were found to be not reported, representing a 1.03% rate of potential missed registration of procedures. Data are collected at different contributing sites by the designated manager of the apheresis center after access is granted to the registry at the site www.waa-registry.org.

2.2 | Data Extraction

All data were anonymous. Data were analyzed as aggregated. For the period covered in this analysis, data had been contributed from a total of 29 centers from 13 countries during the analysis period, (January 1, 2012 to December 31, 2023), for a total of 12 years. Based on approved registry criteria, patients are informed of the registry's purpose and function and asked for consent to allow collection of his/her data regarding the treatment procedure and outcome criteria. The Swedish Ethical Authority has evaluated the registry and decided that follow-up evaluations are time independent (in contrast to a time-limited research project with a specific hypothesis), which is in line with the treatment quality assessment registry intention (Dnr 2024–02687-01, date 2024-05-29).

2.3 | Data Analysis and Statistics

When appropriate, a small number of procedure subtypes were merged into a single group for similar procedures, and diseases and conditions were similarly merged into a single diagnostic code, such as for cell collection/removal including the collection of stem cells for transplantation (SCT), mononuclear cells or removal

of various cells, for instance leukocytes/blasts and erythrocytes. Most tables display a top list, while the data show the overall numbers that used Spectra Optia for any therapeutic approach during the observation period. Some information gaps existed for variables such as diagnosis, (since not all patients received a clear diagnosis), adverse events (since sometimes no registration was done, but not was interpreted as a lack of AE), some with a grading of severity of AE but no symptoms recorded and others vice versa. Replacement fluid was reported in regard to albumin, dextran, and various plasma compounds, or combinations of these. In procedures of cell collection and immunoadsorption fluid was added as an anticoagulant or just as an additive.

Due to the complexity of the data and the lack of other data details like patient co-morbidities and disease condition severity, descriptive statistics were deemed to be most appropriate to summarize the data. This method allows for the identification of important patterns and trends without making assumptions about the relationship between variables. This minimizes the risk of drawing inappropriate inferences and minimizes the potential impact of confounders. Total numbers and percentages were calculated for categorical variables to provide an overview of the sample distribution. Statistical analysis was performed using R Statistical Software (v4.1.2; R Core Team 2021) using the package Tidyverse. Figures were generated using R Statistical Software (v4.1.2; R Core Team 2021) using packages ggplot and gt. The prepared figures and the data analysis are descriptive in nature, without formal statistical comparisons having been performed. A linear regression analysis was conducted to examine trends in adverse event rates (percentage) over the years. Apparent differences observed over time or between centers should be interpreted with caution as they may originate from unaccounted confounding factors. Symptoms of AEs were monitored, and when reported by the patient or staff, scored based on previously established criteria [14]. Mild AEs allowed the procedure to complete uninterrupted without need for medication. Moderate AEs allowed the procedure to be completed without interruption but with the administration of medication. Severe AEs necessitated an interruption in the apheresis procedure to manage the AE and may or may not have been discontinued.

3 | Results

Our analysis of the WAA Registry data for the full 12 years (2012–2023) identified 51 576 apheresis procedures in 13 002 patients, performed exclusively on the Spectra Optia out of 125 657 procedures

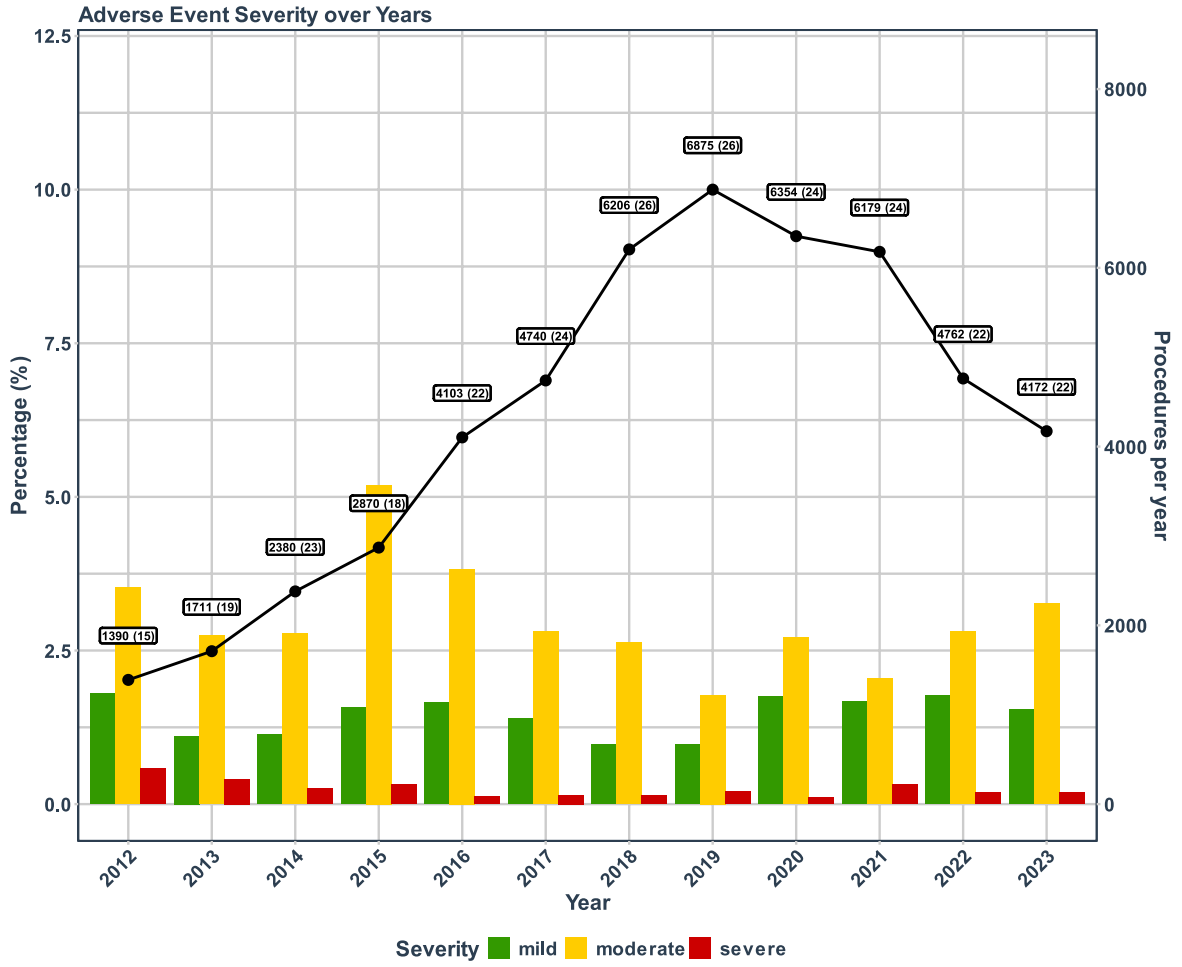

FIGURE 1 | Adverse event severity over years. This figures primary *y*-axis shows the distribution of adverse event percentages (%) by severity across the years 2012 to 2023, as recorded in the registry. Adverse events are categorized by severity: Mild (green), moderate (yellow), and severe (red). The secondary *y*-axis represents the total number of recorded procedures per year, depicted as a scatter plot in black. Each data point is labeled with the total number of procedures and, in parentheses, the number of participating centers for that year.

TABLE 1 | The 20 most frequent therapeutic apheresis procedures on Spectra Optia.

Procedure	Number	% Total procedures
Plasma exchange (centrifugation)	26 740	52.93%
Peripheral Blood Stem Cells- autologous	6099	12.07%
ExtraCorporeal PhotochemoTherapy (ECPT)	4428	8.77%
Leukapheresis (Mononuclear) autologous	2740	5.42%
DONOR Peripheral Blood Stem Cells- Allogeneic	1559	3.09%
Exchange of Erythrocytes	1387	2.75%
Cascade filtration	918	1.82%
IgG adsorption Globaffin column	863	1.71%
IgG adsorption, Sheep antibody	749	1.48%
LDL removal, adsorption	732	1.45%
Protein A adsorber	676	1.34%
Erythrapheresis	576	1.14%
Depletion of Erythrocytes	522	1.03%
ABO-mismatch, Anti A-adsorption	420	0.83%
Leukapheresis (Mononuclear) allogeneic	413	0.82%
Reduction of polymorphonuclear leukocytes if too many	244	0.48%
Leukapheresis by Filtration/ adsorption	234	0.46%
Leukapheresis (Monomorphonuclear) CAR-T	222	0.44%
Leukapheresis (Polymorphonuclear) autologous	149	0.29%
Depletion of Mononuclear cells due to disease	130	0.26%
Other[a]	717	1.42%

[a]Other is a cumulative total of all other procedures with their average percentages.

in total, (41.0% of all procedures analyzed). On average, 4298 procedures were performed on Spectra Optia per year. On average, 22 centers participated in registry reporting annually. Analysis revealed 53.4% of Optia procedures were performed on male patients compared to 46.6% female patients. Median age 55 years (between 0 and 94 years, of whom 5.6% were 0–18 years).

3.1 | Total AE Distribution by Year

The total adverse events (AEs) in the WAA registry for procedures carried out on the Spectra Optia were distributed by severity and the year recorded in the Registry (Figure 1). Mild AE rates were consistent over the period analyzed, ranging between 1%–2%. Moderate was more variable, ranging between 2%–5%. Severe AE rates appeared consistent over the period analyzed, remaining below 0.5%, (Figure 1). We calculated an average of 1.43% mild, 2.81% moderate, and 0.21% severe AE rates for the period analyzed. Within the data set, we noted one patient death where the impact of the apheresis procedure could not have been ruled out. This case, described in a previous report, was an elderly, severely ill patient, who died from myocardial infarction proximate to the apheresis procedure [13].

A linear regression analysis was conducted to examine trends in adverse event rates (percentage) over the time period of 2012 to 2023 across the different adverse event severities. For each severity group, we modeled the relationship between the rate of adverse events and the year. *p*-values were derived using a *t*-test for the slope, which tests the null hypothesis that the slope is zero (no trend). Our analysis revealed a significant decreasing trend in the severe group (slope = −0.023%, *p*-value = 0.0455), indicating a statistically significant reduction in the severe adverse event rate from 2012 to 2023. No significant trends were observed in the mild or moderate severity groups.

3.2 | Top 20 Apheresis Procedures Ranked

Data were analyzed to prepare a list of the 20 most frequent apheresis procedures, by specific protocol (Table 1). AEs for each protocol were rank ordered by total number, with the corresponding number of procedures and percentage of total for each. The top three procedures performed on Spectra Optia are therapeutic plasma exchange, 52.9% (26 740), PBSC collection-autologous, 12.1% (6099), and leukocytapheresis for the purposes of extracorporeal photochemical therapy-photopheresis, 8.8% (4428). These three procedures accounted for nearly three-quarters of all procedures performed on Spectra Optia within the WAA database.

3.3 | Top 20 Diagnoses Ranked

Apheresis procedures were next organized by diagnosis associated with each procedure, (Table 2). The three most common procedures treated using the Spectra Optia were thrombotic thrombocytopenic purpura, (TTP) using plasma exchange, 19.0% (9819), myasthenia gravis, (MG) using plasma exchange, 7.5% (3867), and multiple myeloma using PBSC collection, autologous, 6.1% (3154).

3.4 | Top Diagnoses Treated by the Top 6 Procedures, Ranked

It is important to establish a reference for the distribution of diagnoses treated within each common TA procedure, (Figure S1). Stem cell collections for SCT were dominated by multiple

TABLE 2 | Top 20 diagnoses (by ICD-10 codes) by apheresis procedure, ranked by procedure count.

Diagnosis by ICD-10 code	Procedure	Number	% Total procedures
Thrombotic Thrombocytopenic Purpura (TTP)	Plasma exchange (centrifugation)	9819	18.98%
Myasthenia Gravis	Plasma exchange (centrifugation)	3867	7.47%
Myeloma, Multiple	Peripheral Blood Stem Cells- autologous	3154	6.10%
Guillan Barre Syndrome Acute	Plasma exchange (centrifugation)	1832	3.54%
Complications of bone marrow transplant	ExtraCorporeal PhotochemoTherapy (ECPT)	1762	3.41%
Solid organ transplant rejection	ExtraCorporeal PhotochemoTherapy (ECPT)	1340	2.59%
Myeloma, Multiple	Leukapheresis (Mononuclear) autologous	1328	2.57%
Donor, Stem cells	DONOR Peripheral Blood Stem Cells- Allogeneic	1131	2.19%
Complications of bone marrow transplant	Plasma exchange (centrifugation)	1126	2.18%
Sickle-cell anemia with crisis, including Hb-SS disease with crisis	Exchange of Erythrocytes	1011	1.95%
Hematologic Diseases Other	Plasma exchange (centrifugation)	918	1.77%
Waldenstrom macroglobulinemia	Plasma exchange (centrifugation)	812	1.57%
Hypercholesterolemia (Hyperlipidemia, Group A)	LDL removal, adsorption	783	1.51%
T-cell lymphoma peripheral	ExtraCorporeal PhotochemoTherapy (ECPT)	778	1.50%
Myasthenia Gravis	IgG adsorption, Sheep antibody	732	1.41%
Glomerulonephritis (other than RPGN), chronic	Plasma exchange (centrifugation)	581	1.12%
Myelitis and Encephalomyelitis	Plasma exchange (centrifugation)	553	1.07%
Hemolytic Anemia, AUTO-IMMUNE	Plasma exchange (centrifugation)	528	1.02%
Lymphoma, unspecified	Peripheral Blood Stem Cells- autologous	509	0.98%
T-cell lymphoma peripheral	Leukapheresis (Mononuclear) autologous	482	0.93%
Other[a]	Other	16 599	32.08%

[a]Other is a cumulative total of all other procedures with their average percentages.

myeloma. The term "Mononuclear cell collections" was utilized for similar diagnoses. The latter procedure may contain stem cell collections. The diagnosis of recipients for allogeneic/donor stem cell collections is not reported. Red blood cell exchange procedures were strongly associated with sickle cell disease. Individually, plasma exchange and ECPT were reported used to treat a wide range of conditions.

3.5 | AE Severity for Top 20 Procedures Ranked

To define the AE profile specific to each therapeutic apheresis procedure type, AE data were organized by severity and ranked by procedure type, (Table 3). Analysis reveals unremarkable differences among severe AE rates for most procedures. Elevated mild and moderate AE rates were noted for autologous and donor stem cell collections.

3.6 | AE Severity for Top 18 Diagnoses Ranked

AE rates organized by diagnosis showed a wide range for mild and moderate AEs, (Table 4), with mild AE rates above 5% reported for donor stem cell collection and non-Hodgkin, B-cell lymphoma, unspecified. We found moderate AE rates above 10% for categories reported as donor stem cell collection and lymphoma unspecified. Diagnoses with the highest rates of severe AEs were observed in Guillain-Barré Syndrome Acute and Waldenström Macroglobulinemia. We considered analyzing AE rates per procedure for top diagnoses, but this was not within

TABLE 3 | Top 20 apheresis procedures by adverse event severity, ranked by procedure count.

Procedure	Mild	Moderate	Severe	Number	% Total procedures
Plasma exchange (centrifugation)	1.02%	1.46%	0.31%	26 740	52.93%
Peripheral Blood Stem Cells- autologous	2.66%	9.12%	0.13%	6099	12.07%
ExtraCorporeal PhotochemoTherapy (ECPT)	0.84%	0.18%	0.05%	4428	8.77%
Leukapheresis (Mononuclear) autologous	1.28%	1.02%	0.07%	2740	5.42%
DONOR Peripheral Blood Stem Cells- Allogeneic	4.43%	16.36%	0.26%	1559	3.09%
Exchange of Erythrocytes	1.08%	0.36%	0.22%	1387	2.75%
Cascade filtration	0.87%	2.18%	0.00%	918	1.82%
IgG adsorption Globaffin column	1.04%	2.55%	0.12%	863	1.71%
IgG adsorption, Sheep antibody	0.13%	0.13%	0.00%	749	1.48%
LDL removal, adsorption	0.00%	1.09%	0.00%	732	1.45%
Protein A adsorber	1.78%	0.59%	0.00%	676	1.34%
Erythrapheresis	0.17%	0.35%	0.00%	576	1.14%
Depletion of Erythrocytes	1.34%	0.38%	0.00%	522	1.03%
ABO-mismatch, Anti A-adsorption	3.10%	5.24%	0.00%	420	0.83%
Leukapheresis (Mononuclear) allogeneic	2.66%	2.42%	0.00%	413	0.82%
Reduction of polymorphonuclear leukocytes	2.46%	2.87%	0.41%	244	0.48%
Leukapheresis by Filtration/adsorption	0.43%	0.00%	0.00%	234	0.46%
Leukapheresis (Monomorphonuclear) CAR-T	1.35%	3.60%	0.00%	222	0.44%
Leukapheresis (Polymorphonuclear) autologous	0.00%	0.00%	0.00%	149	0.29%
Depletion of Mononuclear cells due to disease	1.54%	3.85%	0.00%	130	0.26%

the scope of the current analysis; however this is something we may consider including in future analyses.

3.7 | AE Severity for Top 10 TPE Procedures Ranked

Since therapeutic plasma exchange is the most common procedure from the Registry by far, we wanted to closely examine AE rates for TPE procedures organized by diagnosis, (Table 5). Here we observe unremarkable AE rates overall, but observed a slightly elevated (> 0.5%) severe AE rate associated with Guillain–Barré syndrome acute and Waldenstrom macroglobulinemia. Notably, the lowest rate of severe AEs for any condition with a recorded event was myasthenia gravis at 0.08%.

3.8 | AE Severity by Vascular Access Type, Ranked

The most common route of vascular access reported was by peripheral vein at 42.5%, (Table 6). The top three vascular access options recorded were peripheral vein, central vein-jugular, and femoral vein, combining for 80.5% of all access. These three categories reported AE rates for mild (< 2.0%), moderate (< 5.0%), and severe (≤ 0.23%). Two vascular access types associated with higher (> 0.5%) severe AE rates, included artery-to-vein and other combinations, with no further details provided.

3.9 | AE Severity by Replacement Fluid Type

Replacement fluid is a variable known to affect TA safety. Therefore, we examined AE rates for all procedures organized by the fluid used, (Table S1). We found 31 372 records where replacement fluids were recorded. Albumin accounted for the largest percentage of replacement fluids reported, at 56.4% of all procedures. We observed unremarkable mild and moderate AE rates across fluid types used. Two fluid categories associated with severe AE rates above 0.5% were prion-reduced plasma and non-frozen stored plasma, and albumin (3.5%) was the only fluid type that recorded a severe AE rate above 1.0%. Analysis of AE rates and severity for each replacement fluid by each procedure type was considered but would generate too many fluid-procedure combinations to be practical. Since this analysis pertains mainly to Spectra Optia device safety, this extended analysis was determined to be of little additional statistical value.

3.10 | All AEs by Category, Organized and Ranked

We next organized the top 10 reported AEs categories by severity among all procedures examined, (Table 7). The most common

TABLE 4 | Top 20 diagnoses by adverse event severity, ranked by procedure count.

Diagnosis by ICD-10 code	Mild	Moderate	Severe	Number	% Total procedures
Thrombotic Thrombocytopenic Purpura (TTP)	0.93%	1.98%	0.36%	9819	18.98%
Myasthenia Gravis	0.78%	0.72%	0.08%	5005	9.67%
Myeloma, Multiple	2.72%	7.88%	0.13%	4482	8.66%
Complications of bone marrow transplant	1.56%	0.38%	0.24%	2888	5.58%
Guillan Barre Syndrome Acute	1.75%	1.53%	0.66%	1830	3.54%
Solid organ transplant rejection	0.00%	0.00%	0.00%	1340	2.59%
T-cell lymphoma peripheral	0.48%	0.24%	0.08%	1260	2.44%
Hypercholesterolemia (Hyperlipidemia, Group A)	0.65%	3.08%	0.00%	1232	2.38%
Donor, Stem cells	5.57%	21.31%	0.18%	1131	2.19%
Sickle-cell anemia with crisis, including Hb-SS disease with crisis	1.48%	0.49%	0.20%	1011	1.95%
Hematologic Diseases Other	0.65%	0.33%	0.00%	918	1.77%
Waldenstrom macroglobulinemia	1.85%	0.74%	0.62%	810	1.57%
Glomerulonephritis (other than RPGN), chronic	0.69%	0.17%	0.17%	581	1.12%
Myelitis and Encephalomyelitis	1.47%	0.73%	0.37%	545	1.05%
Hemolytic Anemia, AUTO-IMMUNE	0.78%	3.50%	0.39%	515	1.00%
Lymphoma unspecified	2.55%	10.41%	0.20%	509	0.98%
Non-Hodgkin lymphoma, B-cell, unspecified	5.01%	6.47%	0.00%	479	0.93%
Multiple Sclerosis	0.90%	0.90%	0.22%	446	0.86%
Cryoglobulinemia (mixed) (Cryoglobulinemia Vasculitis)	0.27%	1.34%	0.54%	373	0.72%
ABO incompatibility—planned Allograft transplantation	1.61%	2.96%	0.27%	372	0.72%

mild AEs were related to tingling, vascular access categories (combined), and hypotension. For moderate AEs, the most common were tingling, (by far the most common), urticaria, and hypotension. For severe AEs, it was again urticaria, hypotension, and tingling, similar to moderate but in a different rank order. Vascular access was mainly only associated with mild AEs.

3.11 | Interruptions for TPE Procedure Only, Organized and Ranked

We organized the top 10 reported AEs, by severity among TPE procedures, (Table S2). These results were similar to the reported AEs for all procedures, shown in Table 7, with the lone exception of Late complication, Other recorded as the third most common. This is not surprising since TPE constitutes the largest procedure by number among this Spectra Optia procedure subset.

3.12 | All Causes of Interruptions of TA Procedures

Finally, we examined all causes of interruptions recorded in the dataset, (Table S3). Here the reports partly coincided with the medical reasons for interruption given before. By far, the most common causes for pausing and interruptions involve blood flow, other fluid flow, tubing, and coagulation/clotting-related difficulties.

4 | Discussion

This report found that the Spectra Optia performs TA procedures with AE rates similar to or below previously published rates across nearly all variables examined. This implies no special safety signals associated specifically with the use of the Spectra Optia Apheresis System, expanding upon recent analyses from the same WAA Registry data [13, 14]. Elevated rates among mild and moderate AEs were found to be associated with only a handful of procedures recorded in the registry. As an example, it is known that first-time autologous and allogeneic donors will often report relatively high rates of mild and moderate AEs during the collection process [15, 16]. This is presumably because they are naïve to the typical discomforts and inconveniences of the collection procedure. In contrast, patients with more experience with TA procedures often report the same AEs but at substantially lower rates. Side effects experienced during stem cell collections could also be associated with the length of the collection procedure and possibly elevated AC exposure or the cell mobilization medication. Since the possibility of an AE increases with the length of the apheresis procedure,

TABLE 5 | Top 10 diagnoses by adverse event severity, ranked by TPE procedure count.

Diagnosis by ICD-10 code	Mild	Moderate	Severe	Number	% Total procedures
Thrombotic Thrombocytopenic Purpura (TTP)	0.93%	1.98%	0.36%	9819	18.98%
Myasthenia Gravis	0.97%	0.86%	0.08%	3831	7.40%
Guillan Barre Syndrome Acute	1.75%	1.53%	0.66%	1830	3.54%
Complications of bone marrow transplant	0.71%	0.71%	0.44%	1126	2.18%
Hematologic Diseases Other	0.65%	0.33%	0.00%	918	1.77%
Waldenstrom macroglobulinemia	1.85%	0.74%	0.62%	810	1.57%
Glomerulonephritis (other than RPGN), chronic	0.69%	0.17%	0.17%	581	1.12%
Myelitis and Encephalomyelitis	1.47%	0.73%	0.37%	545	1.05%
Hemolytic Anemia, AUTO-IMMUNE	0.78%	3.50%	0.39%	515	1.00%
Multiple Sclerosis	0.90%	0.90%	0.22%	446	0.86%

TABLE 6 | Vascular access type by adverse event severity, ranked by procedure count.

Vascular access type	Mild	Moderate	Severe	Number	% Total procedures
Peripheral vein to peripheral vein	1.85%	4.07%	0.21%	21 997	42.51%
Central vein: jugular (double lumen) to Central vein: jugular	1.09%	2.09%	0.23%	10 761	20.80%
Femoral vein (double lumen) to Femoral vein	1.08%	2.25%	0.19%	8885	17.17%
Central vein: subclavian (double lumen) to Central vein: subclavian	1.39%	1.89%	0.24%	4668	9.02%
AV-fistula to AV fistula	0.35%	0.19%	0.04%	2593	5.01%
AV-graft to AV-graft	0.40%	0.20%	0.00%	498	0.96%
Artery to Vein	2.76%	4.60%	0.69%	435	0.84%
POWERFLOW Implantable Apheresis IV Port, BARD	0.51%	0.76%	0.00%	394	0.76%
Other (Specified)	3.16%	1.05%	0.26%	380	0.73%
Port a Cath double lumen	0.00%	0.00%	0.45%	224	0.43%
Information missing	2.67%	1.07%	0.53%	187	0.36%
Central vein: jugular (double lumen) to peripheral vein	1.09%	1.09%	0.55%	183	0.35%
Femoral vein (double lumen) to peripheral vein	0.56%	4.49%	0.00%	178	0.34%
Central vein: subclavian (double lumen) to peripheral vein	1.48%	0.00%	0.00%	135	0.26%
Other combinations (Specify e.g., from peripheral vein to Central jugular)	4.03%	0.81%	0.81%	124	0.24%
Vortex VX	1.54%	0.00%	0.00%	65	0.13%

we considered normalizing AE rates to the length of the procedure; however, this variable is not currently recorded in the Registry. Likewise, we recognize the potential value of comparing AE rates and severity across variables when normalized for patient acuity and procedure type. The feasibility of collecting information on variables like the procedure time and patient acuity is being considered for future Registry updates. These differences and expectations should also be noted by clinicians when ordering and performing therapeutic apheresis. By better understanding this factor in AE reporting, clinicians can be better prepared to address and mitigate the higher anticipated rate among this subset of patients. Overall, few reasons for technical problems of the Spectra Optia device caused interrupted treatments while access problems were more common. The variation of adverse events appears between factors such as diagnoses, replacement fluids, anticoagulation and inter-center differences

TABLE 7 | Top adverse event types by severity, ranked by procedure count.

Adverse event	Number	% Total
Mild		
Tingling, stitching (signs of low Ca)	214	27.80%
Access- other problems (specify)	145	18.60%
Access- Angiospasm (needs new puncture)	83	10.80%
Hypotension (drop more than 40 mmHg or < 90 mmHg systolic)	73	9.50%
Nausea and/or vomiting	49	6.40%
NA: (Information lacking)	36	4.70%
Urticaria, conjunctivitis	21	2.70%
Technical—other (specify)	18	2.30%
Access- hematoma	17	2.20%
Technical- coagulation in tubing	16	2.10%
Moderate		
Tingling, stitching (signs of low Ca)	1077	68.00%
Urticaria, conjunctivitis	159	10.00%
Hypotension (drop more than 40 mmHg or < 90 mmHg systolic)	72	4.50%
Nausea and/or vomiting	50	3.20%
NA: (Information lacking)	51	3.20%
Technical- coagulation in tubing	17	1.10%
Chills and fever (above 38°C)	17	1.10%
Abdominal pain	13	0.80%
Flush	12	0.80%
Access- other problems (specify)	11	0.70%
Severe		
Urticaria, conjunctivitis	30	22.40%
Hypotension (drop more than 40 mmHg or < 90 mmHg systolic)	24	17.90%
Tingling, stitching (signs of low Ca)	9	6.70%
Access- other problems (specify)	8	6.00%
Chills and fever (above 38°C)	6	4.50%
NA: (Information lacking)	6	4.50%
Bronchospasm	5	3.70%
Flush	4	3.00%
Late complication, Other, specified	4	2.90%
Epilepsia, unspecified	3	2.20%

that are beyond the technical issue [17]. One such variable found to be associated with the highest rate of severe AEs, (above 1.0%), was the use of albumin at 3.5% as the replacement fluid. Albumin at this concentration was reported previously to be associated with an excessively high AE rate, due to an elevated rate of hypotension reactions [17]. Since numerous diseases are influencing the vascular tonus and autonomic nervous system of the patient there may appear a delay in vascular constriction and cardiac response upon hypovolemia, especially if the replacement fluid infused is lagging. Apheresis providers should strongly consider using 5% albumin when such risk is expected, and especially when serum albumin is lowered due to the underlying disease.

This analysis draws from the largest pool of device-specific therapeutic apheresis safety data available and confirms that no new rare or unusual safety signals exist that are associated with the Spectra Optia. Once published, we hope that clinicians will conveniently be able to compare their in-house experience with the results from this study. These results, however they might support TA safety in general, may not be generalizable globally. Regional differences exist in the preferred methods of vascular access, availability of replacement fluid types, anticoagulants used, and the conditions treated using the same TA protocols. When comparing the WAA registry data, (primarily a Nordic registry with additional European, African and Australian centers), to the results from Kundrapu, et al., (from a large hospital system in the US Midwest), we find differences in the types and frequency of conditions treated, the types of TA procedures performed, and the AE rates associated with each procedure [9]. For example, Kundrapu et al. reports a much higher percentage of red blood cell exchange procedures to treat sickle cell disease, and with no reports of apheresis associated with ECPT, presumably due to the regulatory status of this procedure in the US. Apparent differences observed over time or between centers should be interpreted with caution as they may originate from unaccounted confounding factors.

Finally, it is important to note that various TA devices are preferred in different regions. These vary by manufacturer and by separation modality. While safety reporting in the literature on various TA systems exists, they often are limited in scope and draw from relatively small data sets, limiting their utility [18–25]. Comprehensive, device-specific safety analyses drawing from a deep pool of procedural data are generally lacking. Therefore, we encourage other stakeholders to undertake similar device-specific and apheresis modality-specific analyses to produce additional safety insights and to stimulate further focus on this important area of research.

5 | Conclusion

Adverse events calculated for over 50000 therapeutic apheresis procedures performed on the Spectra Optia found AE rates similar to or lower than rates reported previously by other institutions and registries. The average rate of serious adverse events was 0.21% while the average mild and moderate AEs were 1.43% and 2.81%, respectively. Patient deaths associated with apheresis are exceedingly rare. Providers should seek device-specific, real-world safety data when it is available and apply the information to minimize patient safety risk during therapeutic apheresis procedures.

Author Contributions

A.H., S.M., and B.S. all contributed to data handling, analysis, and scientific writing. Acknowledged individuals have participated in initiation and development of the registry, data catch, providing anonymous data and secure patient "safety," evaluation of data content, interpretation, and adherence to performance and approving to the scientific content of the manuscript. The additional authors contributed to the setting of the registry, data catch, check of validity of interpretation of data content in relation to the activities at each center, and approval of manuscript content and to participate as a co-authors.

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Conflicts of Interest

A.H. and S.M. are employees of Terumo Blood and Cell Technologies, manufacturer of the Spectra Optia Apheresis System.

Data Availability Statement

The data that support the findings of this study are available from the World Apheresis Association Registry. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of [third party].

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Top 6 protocol use in percentage, by disease. **Table S1:** Replacement fluid by adverse event severity, ranked by procedure count. **Table S2:** Top adverse event types by severity, ranked by procedure count, (TPE only). **Table S3:** All causes of interruption of apheresis procedure, ranked by count.