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Nationwide Multicenter Analysis of Transfusion Reactions: Real-World Hemovigilance Data from Türkiye

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Article

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Abstract

Türkiye introduced national hemovigilance in 2016, but no multicenter analysis of transfusion reactions has been published. We characterized reaction types, predictors of severity, temporal and inter-center variation, and within-patient recurrence.After excluding 361 pre-2020 reports, all reports from January 2020 to December 2022 were analyzed (N = 11,500; 7,325 patients; 18 regional blood centers). Severity (ISBT grade ≥ 2) was modeled with generalized estimating equations (GEE) with patient-level clustering. Fatal cases combined grade-4 severity at reporting and death at verification. Repeat reactors were identified by proxy matching on birth date, sex, and blood group.Allergic reactions made up 64.1% of reports and FNHTR 16.6%. FFP accounted for 42.3% of implicated components and was strongly linked to allergic reactions (86.3%; GEE OR 4.96 vs. RBC). Severe reactions totaled 670 (5.8%); 65 verification-stage deaths and 66 reconciled fatal cases were recorded. In the base model, severity rose with age ≥ 65 (OR 1.89; 95% CI 1.46–2.44), ABO group O (1.41; 1.12–1.77), group B (1.50; 1.12–1.99), bedside filtration (1.28; 1.03–1.58), and incompatible crossmatch (3.00; 1.97–4.57). After adjustment for reaction type, groups O and B persisted and female sex became protective, whereas crossmatch attenuated (1.73; p = .058). FNHTR fell from 18.7% to 15.3% (p < 0.001) alongside bedside filtration (28.8% to 17.7%). In the extended recurrence-matching frame, 1,440 repeat reactors among 7,608 patients contributed 48.0% of reports; 87.2% of those with > 10 episodes were monotypic, with no escalation in severity (OR 1.008; p = 0.121). Türkiye's hemovigilance profile was marked by FFP-associated allergic reactions, center-level variation, and concentrated recurrence. Targeted management of repeat reactors may reduce a disproportionate share of the reporting burden.

INTRODUCTION

Blood transfusion has been one of the widely used therapeutic procedures in hospital medicine. Each year, millions of the components are administered around the world, and although modern testing has made the practice far safer than it once was, adverse reactions are still occurring in roughly 0.2–1.0% of the units that are transfused [1–3]. In order to detect and to analyze such reactions in a systematic way, the World Health Organization defined hemovigilance as a set of procedures for the surveillance of the entire chain from donation to recipient follow-up [4]. France was among the first countries to set up a national system of this kind, doing so in the early 1990s after contaminated-product crises had exposed the need for structured monitoring of the outcomes of transfusion [5]. Similar programs soon followed in the United Kingdom, in the Netherlands, in Germany, and in Switzerland [3, 5–7]. By 2016, more than 30 countries had contributed data to the ISTARE platform of the International Haemovigilance Network, even though the depth of the reporting and the definitions that were applied varied widely [8, 9].

Accumulated data from these registries are now shaping much of what is known about how often and in what forms transfusion reactions occur. Between 2013 and 2018 in the United States, the Hemovigilance Module of the National Healthcare Safety Network captured reports on over one million components per year [2]. Roughly one in every 455 of the transfused components was associated with an adverse reaction. Allergic reactions made up the largest share of all the reports, and FNHTR stood at the second

most frequent category. From Germany, data over a comparable period showed a similar picture: serious reactions at a grade of 2 or higher constituted about 7–9% of the events that were reported [3, 6]. The rate of fatalities stood at about 0.001% per product. Findings from the Dutch TRIP registry, from an active surveillance program in Spain, and from single-center series in Morocco, India, Iran, and China have all been broadly consistent [7, 10–14]. In virtually every setting, mild allergic reactions and FNHTR together make up the majority of the reports. Serious pulmonary complications, including TACO and TRALI, are infrequent but they contribute disproportionately to the burden of mortality. Besides the overall distribution of the types of reactions, analyses at the registry level have identified profiles that differ according to the component that was transfused. In most of the series, platelets carry the highest rate of reactions per unit, with allergic reactions predominating [14–16]. Concentrates of red blood cells (RBCs), by contrast, are more heavily weighted toward FNHTR. Fresh frozen plasma (FFP) and other products that contain plasma have been associated with both allergic and anaphylactic reactions. Of note, a Dutch comparison of FFP and solvent/detergent-treated plasma showed a noticeable reduction in the rate of allergic and anaphylactic events with the latter product [17]. With regard to the predictors of severity, advanced age, critical illness, high-volume transfusion, and incompatibility of ABO or of minor antigens have each been found to be independent risk factors for serious outcomes [18–21]. Formal modeling that uses standardized grading according to the ISBT scale has, even so, been carried out in few of the published analyses.

One area that has so far received little systematic attention is the recurrence of transfusion reactions within the same patient. Examining 87 patients at one center, Hsieh et al. found that 68% of those with recurrent acute reactions had the same type of reaction at each subsequent exposure, predominantly FNHTR associated with RBC products [22]. In a more recent series, 35% of 53 patients with a history of severe allergic reactions to transfusion were found to have had multiple episodes over 3,221 encounters [23]. Apart from these two institutional studies, together with scattered case reports on recurrent delayed hemolytic reactions in patients who have sickle cell disease, registry-level data on the recurrence of transfusion reactions are essentially absent [24, 25]. As a result, several questions that carry practical weight have not been answered at the population level: whether repeat reactors constitute a stable subgroup, whether severity escalates over successive episodes, and how the classification of a reaction changes from one recurrence to the next.

In Türkiye, a national system of hemovigilance was introduced in 2016 under the National Hemovigilance Guideline (Version 1), which was then updated in 2020 (Version 2); the definitions in both versions are aligned to the standards of the ISBT and of the International Haemovigilance Network [26, 27]. Published data from Türkiye on the subject are, however, limited to single-center retrospective series. The largest of these reported 34 pediatric reactions over seven years at a tertiary hospital [28]. No multicenter or registry-based analysis has so far appeared in the peer-reviewed literature. Our study was designed to address that gap. Analyzing 11,500 transfusion reaction reports submitted between 2020 and 2022 from 18 regional blood centers, after exclusion of 361 pre-2020 records from the registry extract, we set out to characterize the distribution of reaction types and implicated blood components, identify predictors of severity by means of multivariable modeling, and examine temporal trends together with inter-center

variation in reporting patterns. In addition, we aimed to quantify the dynamics of within-patient recurrence: the consistency of reaction type across episodes, the trajectory of severity over successive exposures, and the degree to which the hemovigilance burden is concentrated among repeat reactors.

RESULTS

The analytic cohort comprised 11,500 transfusion reaction reports submitted between January 2020 and December 2022 by 18 regional blood centers across Türkiye, representing 7,325 unique patients (361 pre-2020 reports were excluded; see Methods). Of the reports, 5,879 (51.1%) involved female recipients, and the median age at the time of the transfusion stood at 46.6 years (IQR 23.7–63.4). Red blood cells and plasma components accounted for 40.8% and 42.3% of the implicated components, respectively, with platelets contributing 15.5%. Bedside filtration was recorded in 22.0% of the transfusions (Table 1).

Table 1
Patient demographics and baseline characteristics (*N* = 11,500)

Characteristic	Value
Total reactions, n	11,500
Unique patients, n	7,325
Sex, female, n (%)	5,879 (51.1)
Sex, male, n (%)	5,621 (48.9)
Age at transfusion, median (IQR), y	46.6 (23.7–63.4)
Infant (0–1 y), n (%)	346 (3.0)
Pediatric (1–18 y), n (%)	1,879 (16.3)
Young adult (18–40 y), n (%)	2,572 (22.4)
Middle-aged (40–65 y), n (%)	4,014 (34.9)
Elderly (≥ 65 y), n (%)	2,645 (23.0)
Age not computable, n (%)	44 (0.4)
ABO group A, n (%)	4,932 (42.9)
ABO group O, n (%)	4,014 (34.9)
ABO group B, n (%)	1,679 (14.6)
ABO group AB, n (%)	778 (6.8)
ABO unknown/not recorded, n (%)	97 (0.8)
Rh-negative, n (%)	1,353 (11.8)
Component: RBC, n (%)	4,689 (40.8)
Component: FFP, n (%)	4,860 (42.3)
Component: Platelets, n (%)	1,779 (15.5)
Component: Other, n (%)	172 (1.5)
Crossmatch compatible, n (%)	5,501 (47.8)
Crossmatch not performed, n (%)	5,682 (49.4)
Crossmatch incompatible, n (%)	317 (2.8)
Bedside filtration used, n (%)	2,526 (22.0)
Transfusion completed, n (%)	5,334 (46.4)

Note. IQR = interquartile range; RBC = red blood cells; FFP = fresh frozen plasma.

Characteristic	Value
Volume transfused, median (IQR), mL	200 (100–300)
Severity: grade 1 (non-serious), n (%)	10,830 (94.2)
Severity: grade 2 (serious), n (%)	528 (4.6)
Severity: grade 3 (life-threatening), n (%)	118 (1.0)
Severity: grade 4 (death), n (%)	24 (0.2)
Severe (grade ≥ 2), n (%)	670 (5.8)
Imputability: definite, n (%)	1,983 (17.2)
Imputability: probable, n (%)	2,971 (25.8)
Imputability: possible, n (%)	4,815 (41.9)
Imputability: unlikely, n (%)	1,255 (10.9)
Imputability: unevaluable, n (%)	476 (4.1)
Verification-stage outcome available, n (%)	8,983 (78.1)
Outcome: complete recovery, n/N (%)	8,796/8,983 (97.9)
Outcome: verification-stage death, n (%)	65 (0.6)
Reconciled fatal cases, n (%)	66 (0.6)
Reaction latency, median (IQR), min	30 (0–75)
Reporting delay, median (IQR), h	13.7 (0.8–49.8)
Note. IQR = interquartile range; RBC = red blood cells; FFP = fresh frozen plasma.	

Distribution of reaction types

Mild allergic reactions accounted for 7,373 reports (64.1%), followed by FNHTR at 1,913 (16.6%) and other or unclassified reactions at 741 (6.4%). Anaphylactic reactions made up 332 reports (2.9%), hypertensive reactions 246 (2.1%), and TAD 228 (2.0%). Hypotensive reactions numbered 196 (1.7%) and viral infections 169 (1.5%). TACO was recorded in 124 reports (1.1%) and TRALI in 45 (0.4%). Acute hemolytic reactions due to ABO incompatibility totaled 74 (0.6%), and those due to alloantibody 59 (0.5%). The full distribution is presented in Table 2.

Table 2
Distribution of transfusion reaction types (*N* = 11,500)

Reaction type	n	%
Allergic	7373	64.1
FNHTR	1913	16.6
Anaphylactic	332	2.9
Hypertensive	246	2.1
TAD	228	2.0
Hypotensive	196	1.7
Viral infection	169	1.5
TACO	124	1.1
Hemolytic, ABO	74	0.6
Hemolytic, allo-Ab	59	0.5
TRALI	45	0.4
Other/unclassified	741	6.4
Total	**11,500**	**100.0**

Note. Classification per ISBT/IHN coding as adopted in the Turkish National Hemovigilance Guideline. Viral infection combines HBV, HCV, HIV, and other viral infection categories. Other categories combined includes hypothermia, hypocalcemia/citrate toxicity, bacterial infection, alloimmunization, air embolism, TRIM, and parasitic infection.

Severity and clinical outcomes

Most reactions were graded as non-serious (grade 1; 10,830/11,500, 94.2%). Severe reactions at grade 2 or higher totaled 670 (5.8%), of which 528 were serious (grade 2), 118 were life-threatening (grade 3), and 24 were coded as death at initial severity assessment (grade 4). The distribution of severity grades across reaction types is presented in Supplementary Table S1. Deaths were also recorded independently at verification. Verification-stage outcome data were available for 8,983 reports (78.1%); complete recovery was documented in 8,796 of these reports (97.9%), and verification-stage death in 65 reports. Using the reconciled fatal-case definition of either initial grade-4 severity or verification-stage death, 66 fatal cases were identified. Median reaction latency was 30 minutes (IQR 0–75), and median reporting delay was 13.7 hours (IQR 0.8–49.8).

Predictors of reaction severity

In univariate analysis, severe reactions (grade ≥ 2) were associated with older age, ABO group O, RBC component, incompatible crossmatch, and bedside filtration use (all p < .05; Supplementary Table S2). In the GEE logistic model without adjustment for reaction type (Model 1), age 65 years or older (OR 1.89; 95% CI 1.46–2.44), ABO group O (OR 1.41; 95% CI 1.12–1.77), ABO group B (OR 1.50; 95% CI 1.12–1.99), bedside filtration (OR 1.28; 95% CI 1.03–1.58), and incompatible crossmatch (OR 3.00; 95% CI 1.97–4.57) were independently associated with severity (Table 4). After additional adjustment for reaction type (Model 2), the effects of age 65 years or older (OR 1.65; 95% CI 1.22–2.22), ABO group O (OR 1.56; 95% CI 1.20–2.04), and ABO group B (OR 1.50; 95% CI 1.08–2.10) remained significant. Female sex was associated with lower odds of severity after reaction-type adjustment (OR 0.78; 95% CI 0.62–0.99), whereas bedside filtration no longer reached statistical significance (OR 1.27; 95% CI 0.99–1.62; p = .062). The incompatible-crossmatch effect was attenuated from OR 3.00 to OR 1.73 (95% CI 0.98–3.06; p = .058), consistent with partial mediation through acute hemolytic reactions (Fig. 1). Component type, Rh status, and AB blood group were not significant predictors in either model.

Table 3. Distribution of reaction types by transfused component (major components only; *N* = 11,328)

Reaction type	RBC, n (%)	FFP, n (%)	PLT, n (%)	Total
Allergic	1,947 (41.5)	4,193 (86.3)	1,139 (64.0)	7,279
FNHTR	1,396 (29.8)	171 (3.5)	313 (17.6)	1,880
Anaphylactic	59 (1.3)	149 (3.1)	113 (6.4)	321
Hypertensive	201 (4.3)	36 (0.7)	8 (0.4)	245
TAD	130 (2.8)	54 (1.1)	33 (1.9)	217
Hypotensive	141 (3.0)	37 (0.8)	16 (0.9)	194
TACO	95 (2.0)	20 (0.4)	8 (0.4)	123
Acute hemolytic	108 (2.3)	15 (0.3)	10 (0.6)	133
TRALI	25 (0.5)	13 (0.3)	6 (0.3)	44
Other	587 (12.5)	172 (3.5)	133 (7.5)	892
Total	4,689	4,860	1,779	11,328

Note. Column percentages in parentheses. RBC = red blood cells; FFP = fresh frozen plasma; PLT = platelets. Minor component types (n = 172) excluded. Overall chi-square = 2,538.2; df = 18; p < 0.001; Cramér's V = 0.334. Other includes viral infections and unclassified categories pooled from Table 2.

Table 4
GEE logistic regression: predictors of severity (grade ≥ 2 vs. grade 1)

Predictor	Model 1 OR	95% CI	p	Model 2 OR	95% CI	p
Female sex	0.89	0.73–1.09	0.259	0.78	0.62–0.99	0.042
Age ≥ 65 y (vs. 40–65)	1.89	1.46–2.44	< 0.001	1.65	1.22–2.22	0.001
Age 18–40 y (vs. 40–65)	0.80	0.58–1.11	0.178	0.93	0.65–1.34	0.697
Age 1–18 y (vs. 40–65)	1.13	0.83–1.54	0.435	1.10	0.74–1.64	0.637
Age 0–1 y (vs. 40–65)	1.04	0.57–1.89	0.907	1.40	0.70–2.83	0.343
ABO group O (vs. A)	1.41	1.12–1.77	0.003	1.56	1.20–2.04	0.001
ABO group B (vs. A)	1.50	1.12–1.99	0.006	1.50	1.08–2.10	0.017
ABO group AB (vs. A)	0.94	0.62–1.43	0.770	0.91	0.54–1.52	0.719
Rh-negative	1.15	0.86–1.53	0.340	1.21	0.88–1.66	0.239
FFP (vs. RBC)	0.83	0.60–1.16	0.288	1.28	0.86–1.89	0.222
Platelets (vs. RBC)	1.11	0.85–1.45	0.456	1.12	0.80–1.57	0.495
Bedside filtration	1.28	1.03–1.58	0.025	1.27	0.99–1.62	0.062
Incompatible crossmatch	3.00	1.97–4.57	< 0.001	1.73	0.98–3.06	0.058

Note. GEE with exchangeable correlation and patient-level clustering (7,256 clusters; 11,456 observations). Model 1: base predictors. Model 2: additionally adjusted for reaction type. Reference categories: male, age 40–65, ABO group A, Rh-positive, RBC, compatible crossmatch, no filtration. OR = odds ratio; CI = confidence interval.

Temporal trends

Reporting volume increased from 3,093 reactions in 2020 to 4,590 in 2022 (Table 5). Over the same period, the proportion of allergic reactions rose from 62.9% to 65.5% (Cochran–Armitage Z = + 2.46; p = 0.014), while the proportion of FNHTR fell from 18.7% to 15.3% (Z = − 3.85; p < 0.001). Anaphylactic

reactions increased from 2.5% to 3.3% (Z = + 2.33; p = 0.020), and TACO decreased from 1.5% to 0.9% (Z = − 2.14; p = 0.032). Hypertensive reactions and TAD both showed significant upward trends. The proportion of severe reactions (grade ≥ 2) remained stable at approximately 5.8% across the three years (Z = + 0.29; p = 0.775). Bedside filtration use declined from 28.8% to 17.7% (Z = − 11.36; p < 0.001), concurrent with the decline in FNHTR. FFP as a proportion of the implicated components rose from 38.5% to 45.5% (Z = + 6.18; p < 0.001). Median reporting delay decreased from 14.2 to 12.3 hours over the period (p = 0.029). The concurrent decline in FNHTR and bedside filtration, with a modest increase in allergic reactions and stable severity proportions, is shown in Fig. 2.

Table 5
Temporal trends in reaction types, severity, and practice variables (2020–2022)

Variable	2020 (n = 3,093)	2021 (n = 3,817)	2022 (n = 4,590)	Z	p
Allergic	1,945 (62.9)	2,421 (63.4)	3,007 (65.5)	+ 2.46	0.014
FNHTR	579 (18.7)	630 (16.5)	704 (15.3)	-3.85	< 0.001
Anaphylactic	76 (2.5)	103 (2.7)	153 (3.3)	+ 2.33	0.020
TACO	45 (1.5)	37 (1.0)	42 (0.9)	-2.14	0.032
Hypertensive	26 (0.8)	89 (2.3)	131 (2.9)	+ 5.83	< 0.001
TAD	34 (1.1)	79 (2.1)	115 (2.5)	+ 4.25	< 0.001
Severe (≥ 2)	175 (5.7)	227 (5.9)	268 (5.8)	+ 0.29	0.775
Bedside filtration	892 (28.8)	820 (21.5)	814 (17.7)	-11.36	< 0.001
FFP use	1,192 (38.5)	1,579 (41.4)	2,089 (45.5)	+ 6.18	< 0.001
Reporting delay, median h	14.2	14.5	12.3		0.029

Note. Values are n (%) unless otherwise stated. Z = Cochran–Armitage test statistic for linear trend. Positive Z indicates an increasing proportion; negative Z indicates a decreasing proportion. Reporting delay compared with the Kruskal–Wallis test. Pre-2020 data (n = 361) excluded.

Inter-center variation

Across the 18 reporting centers, the proportion of allergic reactions ranged from 50.5% to 92.6%, FNHTR from 0.0% to 31.9%, anaphylactic reactions from 0.0% to 8.1%, and severe reactions from 0.5% to 16.1% (**Supplementary Table S4**). Median reporting delay varied from 0.5 to 63.6 hours between centers. In a GEE model adjusted for age, sex, and component type, İzmir showed the highest center-level severity after case-mix adjustment (OR 1.95; 95% CI 1.37–2.76; p < 0.001), followed by Adana (OR 1.51; 95% CI 1.02–2.25; p = 0.041). Ankara and İstanbul had elevated odds that did not reach statistical significance.

Repeat reactors

Repeat-reactor patterns were examined in an extended recurrence-matching frame rather than only in the restricted 2020–2022 descriptive cohort. This frame included 11,858 reports with sufficient proxy identifiers from the original registry extract and yielded 7,608 estimated unique patients. Among them, 1,440 patients (18.9%) had two or more reported reactions; together, they contributed 5,690 episodes, accounting for 48.0% of all reports in the extended recurrence-matching frame (Fig. 3; Table 6, Panel A). At the extreme of the distribution, 94 patients with more than 10 episodes each contributed 1,881 reactions (15.9% of the total). Compared with single reactors, repeat reactors were younger (median age 44.4 vs. 48.3 years; $p < 0.001$), more often male (51.7% vs. 46.1%; $p < 0.001$), and had a considerably higher proportion of FFP-associated reactions (56.2% vs. 28.7%; $p < 0.001$). Allergic reactions were more frequent among repeat reactors (69.6% vs. 59.2%; $p < 0.001$), while FNHTR was less frequent (11.9% vs. 20.9%; $p < 0.001$). Per-episode severity was higher in repeat reactors (6.9% vs. 4.9%; $p < 0.001$), but mortality per episode was lower (0.42% vs. 0.75%; $p = 0.029$).

Table 6. Repeat-reactor characteristics

Panel A. Episode distribution

Episodes per patient	Patients, n	Patients, %	Reactions, n	Reactions, %	Cumulative reactions, %
1 (single)	6,168	81.1	6,168	52.0	100.0
2	902	11.9	1,804	15.2	48.0
3–5	338	4.4	1,193	10.1	32.8
6–10	106	1.4	812	6.8	22.7
>10	94	1.2	1,881	15.9	15.9

Panel B. Reaction-type consistency among repeat reactors

Episode count	n patients	Monotypic, n (%)	Polytypic, n (%)	Mean dominant, %
2 episodes	902	576 (63.9)	326 (36.1)	81.9
3–5	338	163 (48.2)	175 (51.8)	77.6
6–10	106	77 (72.6)	29 (27.4)	88.9
>10	94	82 (87.2)	12 (12.8)	95.9

Note. The table is based on an extended recurrence-matching frame that included 11,858 reports yielding 7,608 estimated unique patients. The broader frame was used as exclusion of pre-2020 reports could reclassify some repeat reactors as single reactors. Panel A: Cumulative reactions % = proportion

of all reactions contributed by patients with that many or more episodes. Panel B: Monotypic = all episodes classified as the same reaction category. Mean dominant % = mean proportion of episodes belonging to the most frequent category for each patient. GEE escalation model (not shown): episode number OR = 1.008; 95% CI 0.998–1.019; p = 0.121.

Among repeat reactors with two episodes, 63.9% were monotypic (Table 6, Panel B). Consistency was highest among patients with more than 10 episodes, of whom 87.2% had the same reaction type at every recorded episode, with a mean dominant-type proportion of 95.9%. Patients with 3–5 episodes showed the lowest monotypic rate (48.2%). In the GEE model testing whether severity escalated over successive episodes, episode number was not a significant predictor after adjustment for age, sex, component type, and reaction type (OR 1.008; 95% CI 0.998–1.019; p = 0.121). In the transition matrix (**Supplementary Table S5**), 80.2% of patients whose first reaction was allergic had an allergic reaction again at the second episode. Among patients whose first episode was classified as anaphylactic (n = 57), only 45.6% recurred as anaphylactic, while 36.8% were reclassified as allergic at the second exposure.

DISCUSSION

Our analysis of 11,500 reports from 18 regional blood centers over 2020–2022 yielded five principal findings. The reaction mix was dominated by mild allergic reactions and FNHTR, shaped in large part by the high share of FFP among implicated components. Reaction profiles diverged sharply by component: FFP was overwhelmingly linked to allergic reactions, RBCs to FNHTR. Severity was independently associated with older age and ABO group O and B; an incompatible crossmatch was strongly associated in the base model but attenuated once reaction type was taken into account. FNHTR and bedside filtration declined together over the three years. In the extended recurrence-matching frame, fewer than one in five patients accounted for nearly half of analyzable reports, with high consistency of reaction type and no escalation in severity across episodes.

At 64.1%, the share of allergic reactions in our registry exceeds that of most established hemovigilance systems. In the US NHSN, allergic reactions accounted for 46.8% of reported events between 2013 and 2018 [2], and German data over a comparable period were similar [3, 6]. FNHTR, by contrast, stood at 16.6% in our data, well below the NHSN's 36.1% [2]. The composition of the transfused components likely explains this asymmetry. FFP made up 42.3% of implicated components in our registry, unusually high by international standards, where RBCs predominate. Since FFP was linked to allergic reactions in 86.3% of cases (GEE OR 4.96 vs. RBC; 95% CI 4.25–5.80), a transfusion mix weighted toward FFP would inflate the allergic fraction and compress FNHTR accordingly. Whether this high rate of FFP use reflects clinical practice, transfusion indications, or product availability is beyond what our data can settle, but it bears on blood-product stewardship policy. Of note, a Dutch comparison of standard FFP and solvent/detergent-treated plasma showed a significant reduction in the rate of allergic and anaphylactic reactions with the latter product [17]. If plasma-related reactions are indeed the primary driver of the burden of reactions in Türkiye, a transition to pathogen-inactivated plasma could plausibly reduce the overall rate of the reported adverse events. Before such a transition were undertaken, it would need to be

evaluated in the context of cost, the logistics of the supply, and the specific indications for which FFP is being prescribed.

With a Cramér's V of 0.334, the strength of the association between the type of component and the category of the reaction was considerable and is consistent with international data, though it was observed here at a scale and in a regulatory environment not previously reported. At a large US center, Yune and O'Brien found that platelets had the highest rate of reactions per unit (0.61%), with allergic reactions predominating, while reactions associated with RBCs were weighted toward FNHTR [15]. Our data are congruent with that pattern. From a Chinese pediatric center, Guo et al. [16] reported a similar hierarchy, and in the NHSN for 2010–2012, Harvey et al. [14] showed comparable distributions. Among platelet transfusions in our registry, anaphylactic reactions were enriched at 6.4% of the platelet-associated reactions (GEE OR 4.31 relative to RBC; 95% CI 3.12–5.96).

Among demographic predictors, age of 65 years or older was the clearest marker of severity, with an OR of 1.89 in Model 1 and 1.65 after adjustment for reaction type. Female sex showed no association in the base model but carried lower odds after reaction-type adjustment; the effect was modest and warrants caution. For incompatible crossmatch, the OR fell from 3.00 in Model 1 to 1.73 ($p = .058$) once reaction type was included, which suggests that much of its effect runs through an association with acute hemolytic reactions. Gehrie et al. [20] and McCullagh et al. [21] have likewise emphasized that ABO and minor-antigen incompatibility are overrepresented among severe and fatal reactions.

Perhaps the most unexpected result was the independent association between severity and recipient ABO group. Relative to group A, groups O and B carried higher odds in both models, while group AB did not. For group O, the OR was 1.41 in Model 1 and 1.56 after reaction-type adjustment; for group B, it was 1.50 in both. The literature on ABO and reaction severity has focused almost entirely on the risk that group O donors pose to non-O recipients through passive transfer of high-titer anti-A and anti-B antibodies [21, 29, 30]. That group O or B recipients might experience more severe reactions has not, to our knowledge, been reported at the population level. One plausible mechanism is that higher baseline isoagglutinin titers in group O individuals amplify immune responses to minor-incompatible plasma in the transfused components. Still, unmeasured comorbidities that track with blood group in the Turkish population could confound the association, so it should be read with caution until other registries replicate it.

Between 2020 and 2022, FNHTR fell from 18.7% to 15.3% of reported reactions ($p < 0.001$), and over the same period recorded bedside filtration declined from 28.8% to 17.7% ($p < 0.001$). The two trends seem contradictory: if bedside filtration prevents FNHTR by removing residual leukocytes, less filtration should yield more FNHTR, not less. The likely explanation is that prestorage leukoreduction was expanding at the processing stage during this period, gradually replacing filtration at the bedside. International natural-experiment studies support this reading. At Yale-New Haven, universal prestorage leukoreduction cut FNHTR by 47% for RBCs and 93% for platelets, with no change in allergic reactions [31]. Yazer et al. [32] reported a comparable reduction after the same policy change, and at Johns Hopkins, King et al. [33]

found FNHTR halved as leukoreduced RBC inventory rose from 4% to 99.5%. In a Berlin hospital-wide comparison, Pruss et al. [34] found that prestorage-filtered RBCs gave the lowest FNHTR rate (0.03%), well below units that had undergone only buffy-coat depletion or post-storage filtration, bearing directly on the bedside-versus-prestorage distinction in our data. The Turkish National Hemovigilance Guideline records leukocyte-reduced components and bedside filtration as component-level variables but sets no directive date for universal prestorage leukoreduction [26, 27], and our data do not indicate whether a given unit was prestorage-leukoreduced. The link between the two declining trends is therefore inferential. Even so, the co-movement mirrors controlled before-and-after studies, and the much larger fall in FNHTR than the slight rise in allergic reactions lends the association some specificity.

Across the 18 reporting centers, the proportion of allergic reactions ranged from 50.5% to 92.6%, FNHTR from 0.0% to 31.9%, and severe reactions from 0.5% to 16.1%. After adjustment for age, sex, and the type of component, İzmir had the highest center-level severity (OR 1.95; 95% CI 1.37–2.76), a difference not attributable to the composition of its patient population. In the international hemovigilance literature, heterogeneity of this kind is well documented. Ackfeld et al. [3] attributed much of the variation in reported reaction rates across European countries to differences in the definitions, in the criteria for the assessment of imputability, and in the intensity of reporting rather than to true differences in clinical risk. Implementation of electronic reporting systems has been shown to increase the rate of reporting of reactions by a factor of 2.5 to 3 without inflating the number of uninterpretable cases [35, 36], a finding that further supports the view that the infrastructure of reporting shapes the data as much as the underlying biology does. In our registry, the wide range of the median reporting delay (0.5 to 63.6 hours between centers) points to heterogeneity in how quickly and how thoroughly the reactions are documented. Standardized training in the classification of reaction types and in the grading of severity across the reporting centers would help to disentangle true clinical variation from artefacts of surveillance practice.

In the extended recurrence-matching frame, the concentration of 48.0% of analyzable reports among 18.9% of patients is, to our knowledge, the first time this pattern has been quantified at a national registry level. Working with 87 recurrent reactors at a single center in Taiwan, Hsieh et al. found that 68% had the same type of reaction on later exposures, mostly FNHTR tied to RBC products [22]. Our data echo that finding and extend it to a much larger scale: among 1,440 repeat reactors, 62.4% were monotypic across all their episodes, and among those with more than 10 episodes the monotypic rate climbed to 87.2%, with a mean dominant-type proportion of 95.9%. Heavy repeaters in our registry thus look like a phenotypically stable subgroup, locked into one type of reaction that is almost always allergic. What one might expect from progressive immunologic sensitization did not materialize: severity did not escalate with successive episodes (GEE OR 1.008 per additional episode; $p = 0.121$). Per-episode severity was higher in repeat reactors than in single reactors (6.9% vs. 4.9%), yet mortality was lower (0.42% vs. 0.75%). That dissociation fits a survivorship effect, patients who die, or whose complications are severe enough to halt further transfusion, never enter the repeat-reactor pool, which leaves behind a selected group whose reactions recur but remain survivable. In a pediatric series, Sanders et al. found that prior febrile reactions modestly raised the odds of a subsequent febrile reaction on univariate

analysis (OR 2.74), but the association did not hold in multivariable models [25], congruent with our GEE result. Clinically, identifying a subset of patients who generate a disproportionate share of the hemovigilance burden matters. Many institutions apply premedication broadly, to every transfusion recipient or to anyone with a single prior reaction. Our data point instead toward a more targeted approach, aimed at the identifiable group of repeat reactors who are phenotypically stable and not escalating in severity, which could be both more efficient and more effective.

Limitations

The registry captured only reported reactions, not all transfusions performed, and because reporting is unlikely to be complete, rates per unit transfused could not be reliably calculated. The association between ABO group O and severity came from a passive surveillance system, so residual confounding by unmeasured clinical variables cannot be ruled out. Variation between centers in how reaction types were classified and severity graded may have introduced systematic biases that case-mix adjustment could not fully correct. The observation window (2020–2022) also overlapped the COVID-19 pandemic, which may have shifted transfusion practice, reporting intensity, and patient case-mix in ways the registry variables do not capture. Finally, the recurrence analysis drew on an extended matching frame rather than the restricted 2020–2022 descriptive cohort; this preserved recurrence histories but leaves its denominators different from those of the main cohort.

CONCLUSIONS

Türkiye's first nationwide hemovigilance analysis shows a reaction profile shaped in large part by the components that were transfused. Plasma made up an unusually high share of them, and allergic reactions dominated at a proportion above most international benchmarks. Severity was associated, independently, with older age and with recipient groups O and B relative to group A. An incompatible crossmatch carried the strongest association in the base model, but much of that effect fell away once reaction type was taken into account, which places most of its weight on acute hemolytic reactions rather than on incompatibility as such. Across the three years, FNHTR and bedside filtration declined together, a pattern consistent with a shift toward prestorage leukoreduction, though our data can only point toward that link, not establish it. Reporting practice varied widely between centers, both in the mix of reactions recorded and in how those reactions were documented, which argues for standardized training in classification. The result carrying the most practical weight is concentration: in the extended recurrence-matching frame, fewer than one in five patients accounted for almost half of all reported reactions. These repeat reactors returned with the same type of reaction and showed no escalation in severity from one episode to the next. Directing preventive effort at that identifiable group could reduce a disproportionate share of the hemovigilance burden.

METHODS

Study design and data source

We conducted a retrospective analysis of all reports of transfusion reactions submitted to the Turkish national hemovigilance system between January 2020 and December 2022. The data were obtained from the Blood and Blood Products Department of the Ministry of Health, which maintains a centralized registry of the adverse reactions reported by hospital blood centers and by transfusion services across Türkiye. Under the National Hemovigilance Guideline (Versions 1 and 2), reporting to the national system is a regulatory requirement for all facilities that administer blood components [26, 27]. At each hospital, the clinical team initiates the report at the time of the reaction and forwards it to the hemovigilance unit, where a physician on the transfusion medicine service reviews the case, assigns the category of the reaction, grades the severity and the imputability, and enters the final classification into the national database. Because reporting volumes during the start-up period were low and inconsistent, reports with transfusion start dates before 1 January 2020 were excluded (n = 361). After this exclusion, the final analytic cohort comprised 11,500 transfusion reaction reports submitted between January 2020 and December 2022 from 18 regional blood centers.

Definitions and classification

Transfusion reactions were classified according to the standard definitions of the International Society of Blood Transfusion (ISBT) in collaboration with the International Haemovigilance Network (IHN), as adopted in the Turkish National Hemovigilance Guideline [26, 27]. In total, 23 categories of reactions were recorded, spanning both acute reactions (those with an onset within 24 hours of the transfusion) and delayed reactions. Among the acute categories were mild allergic reaction (A5), febrile non-hemolytic transfusion reaction (FNHTR, A4), anaphylactic reaction (A6), acute hemolytic reaction due to ABO incompatibility (A1) or to alloantibody (A2), non-immune hemolysis (A3), TRALI (A7), transfusion-associated dyspnea (TAD, A8), TACO (A9), hypotensive reaction (A10), and hypertensive reaction (A11). Among the delayed categories were delayed hemolytic transfusion reaction (DHTR, G1), delayed serologic reaction (G2), post-transfusion purpura (G4), and hemosiderosis (G5).

Grading of severity followed a four-point scale in accordance with the definitions of the ISBT: grade 1 (non-serious), grade 2 (serious), grade 3 (life-threatening), and grade 4 (death attributable to the reaction). For the multivariable analyses, the outcome of severity was dichotomized into non-severe (grade 1) and severe (grades 2 through 4). Imputability was scored on a four-level scale: 0 (excluded or unlikely), 1 (possible), 2 (probable), and 3 (definite). Records in which the imputability could not be assessed were retained in the dataset but coded separately.

Data processing and derived variables

Standard quality checks were applied to the raw data before the analysis. Coding inconsistencies in the blood-group field were corrected, and ABO group and Rh type were separated into distinct variables. Records with implausible values for transfusion volume or duration (e.g., zero, negative, or in excess of 24 hours) were set to missing for the affected variable. Reports submitted before 2020 were excluded at the cohort-definition stage, but no additional reports were removed because of these data-cleaning corrections. Age at the time of transfusion was calculated from date of birth and transfusion start date.

In 44 reports, age could not be validly computed because the recorded birth date was later than the transfusion date; these reports were retained and classified as age not computable in descriptive tables. Patients were classified into five age groups: infant (0–1 year), pediatric (1–18 years), young adult (18–40 years), middle-aged (40–65 years), and elderly (≥ 65 years). Reaction latency was computed as the interval in minutes between the start of the transfusion and the recorded onset of the reaction; reporting delay was computed as the interval in hours between the onset and the formal submission of the report. Blood components were grouped into broad categories: red blood cells (RBCs), fresh frozen plasma (FFP), platelets, cryoprecipitate, immune plasma, granulocytes, and whole blood. The region of the reporting center was derived from the name of the supplying blood center.

Patient identification and repeat-reactor classification

Unique patients were estimated through proxy matching of birth date, sex, and blood group. For the main 2020–2022 analytic cohort, this procedure identified 7,325 unique patients. Because exclusion of pre-2020 records could truncate recurrence histories and misclassify prior repeat reactors as single reactors, the repeat-reactor analysis was conducted as an extended recurrence-matching subanalysis using all registry reports with sufficient proxy identifiers from the original extract. In this extended recurrence-matching frame, 7,608 patients contributed 11,858 analyzable reports; 1,440 patients with two or more reported reactions were classified as repeat reactors.

Statistical analysis

For categorical variables, descriptive statistics were reported as counts with proportions. For continuous variables, medians with interquartile ranges (IQR) were reported in view of the right-skewed distributions of age, volume, duration, reaction latency, and reporting delay. Between groups, comparisons were carried out with the chi-square or Fisher exact test for categorical variables and with the Mann–Whitney U or Kruskal–Wallis test for continuous variables. Because patients could contribute more than one report to the dataset, the observations were not independent of one another. To account for this clustering, all multivariable models were fitted by means of generalized estimating equations (GEE) with an exchangeable working correlation structure and patient-level clusters. Five sets of GEE models were estimated. In the first set, to examine the association between the type of component and the category of the reaction, separate binary GEE logistic models were fitted for each of the five most frequent reaction types (allergic, FNHTR, anaphylactic, TACO, and acute hemolytic); the covariates in these models were component type, age, sex, Rh status, and bedside filtration. In the second set, to identify predictors of severity, a GEE logistic model was fitted with severity (grade ≥ 2 vs. grade 1) as the outcome and age group, sex, ABO group, Rh status, component type, crossmatch result, and bedside filtration as predictors (Model 1); a second specification additionally adjusted for the type of the reaction (Model 2) in order to assess whether the effects of the other predictors were mediated through reaction type. Deaths were recorded in two registry fields: initial severity grade and verification-stage clinical outcome. For fatality analyses, a reconciled fatal-case indicator was defined as either grade-4 severity at initial reporting or death recorded at verification. In the 2020–2022 cohort, 24 reports were coded grade 4 at initial reporting, 65 had verification-stage death, and 66 met the reconciled fatal-case definition.

Temporal trends in reaction types, bedside filtration, and severity across the three years were tested with Cochran-Armitage tests for linear trend. To assess inter-center variation, we tabulated the proportions of allergic reactions, FNHTR, severe events, and reporting delay by center, then fitted a GEE model with the five highest-volume centers as fixed effects alongside case-mix covariates, testing whether center-level differences in severity survived adjustment. For the component-by-reaction table, adjusted standardized residuals identified cell-level associations beyond chance, and Cramér's V summarized the overall strength of association. For the repeat-reactor analysis, single and repeat reactors were compared on their demographic and clinical characteristics. In order to test whether the severity of reactions escalated over successive episodes, a GEE logistic model was fitted with severity as the outcome and episode number (treated as a continuous variable) as the primary predictor, adjusting for age, sex, the type of component, and the type of reaction, with patient-level clustering. Statistical analyses were performed in IBM SPSS Statistics, version 29.0 (IBM Corp., Armonk, NY, USA), with figure generation and data visualization performed in Python. Two-sided p-values below 0.05 were considered statistically significant.

Declarations

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Author Contributions:

Conceptualization, H.D., Ö.A.İ. and S.P.; methodology, H.D. and S.P.; software, S.P.; validation, H.D., Ö.A.İ. and S.P.; formal analysis, S.P.; investigation, H.D.; resources, H.D.; data curation, H.D. and S.P.; writing—original draft preparation, S.P.; writing—review and editing, H.D., Ö.A.İ. and S.P.; visualization, S.P.; supervision, H.D.; project administration, H.D. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement:

The data used in this study are derived from the Turkish Ministry of Health National Hemovigilance Registry and are not publicly available due to regulatory restrictions. Requests to access the aggregated data should be directed to the Blood and Blood Products Department, Turkish Ministry of Health.

Competing Interests

The authors declare no competing interests.

Informed Consent Statement:

Patient consent was waived due to the retrospective, de-identified, registry-based nature of the study. No direct patient contact or intervention was involved.

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Conflicts of Interest: The authors declare no conflicts of interest.

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Figures

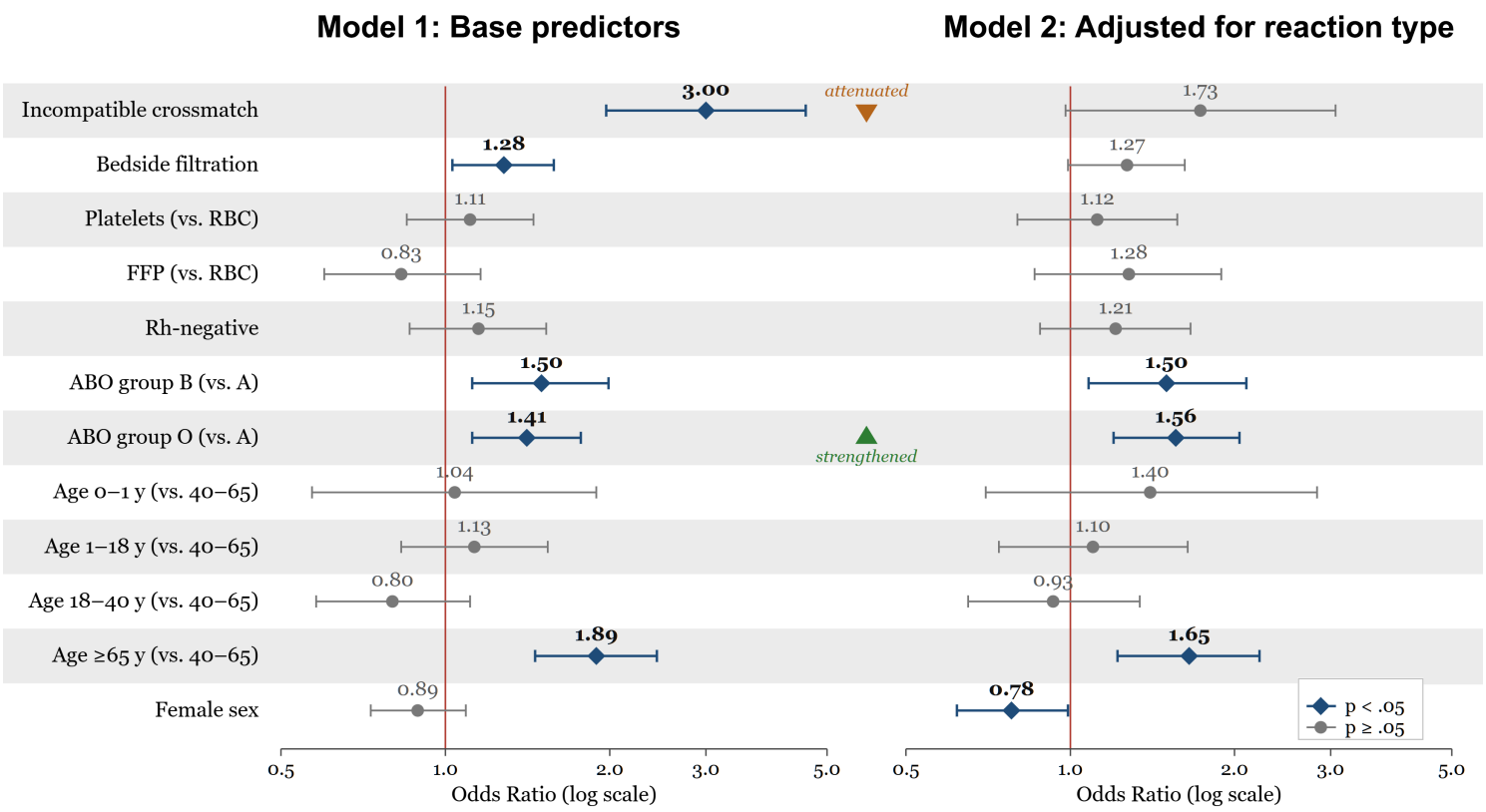


Figure 1

Forest plot of GEE logistic regression predictors of severity (grade ≥2 vs. grade 1). Model 1 (left): base predictors. Model 2 (right): additionally adjusted for reaction type. Diamond markers (blue) indicate p < .05; circle markers (grey) indicate p ≥ .05. Odds ratios are displayed above each point estimate; horizontal lines represent 95% confidence intervals. The vertical red line marks OR = 1.0 (no effect). Between panels, ▼ marks the attenuation of the incompatible-crossmatch effect (3.00 → 1.73) and ▲ marks the modest strengthening of the ABO group O effect after adjustment for reaction type (1.41 → 1.56). Female sex became significant after adjustment for reaction type, whereas bedside filtration no longer reached statistical significance. ABO group AB was included in the model but omitted from the plot for visual compactness.

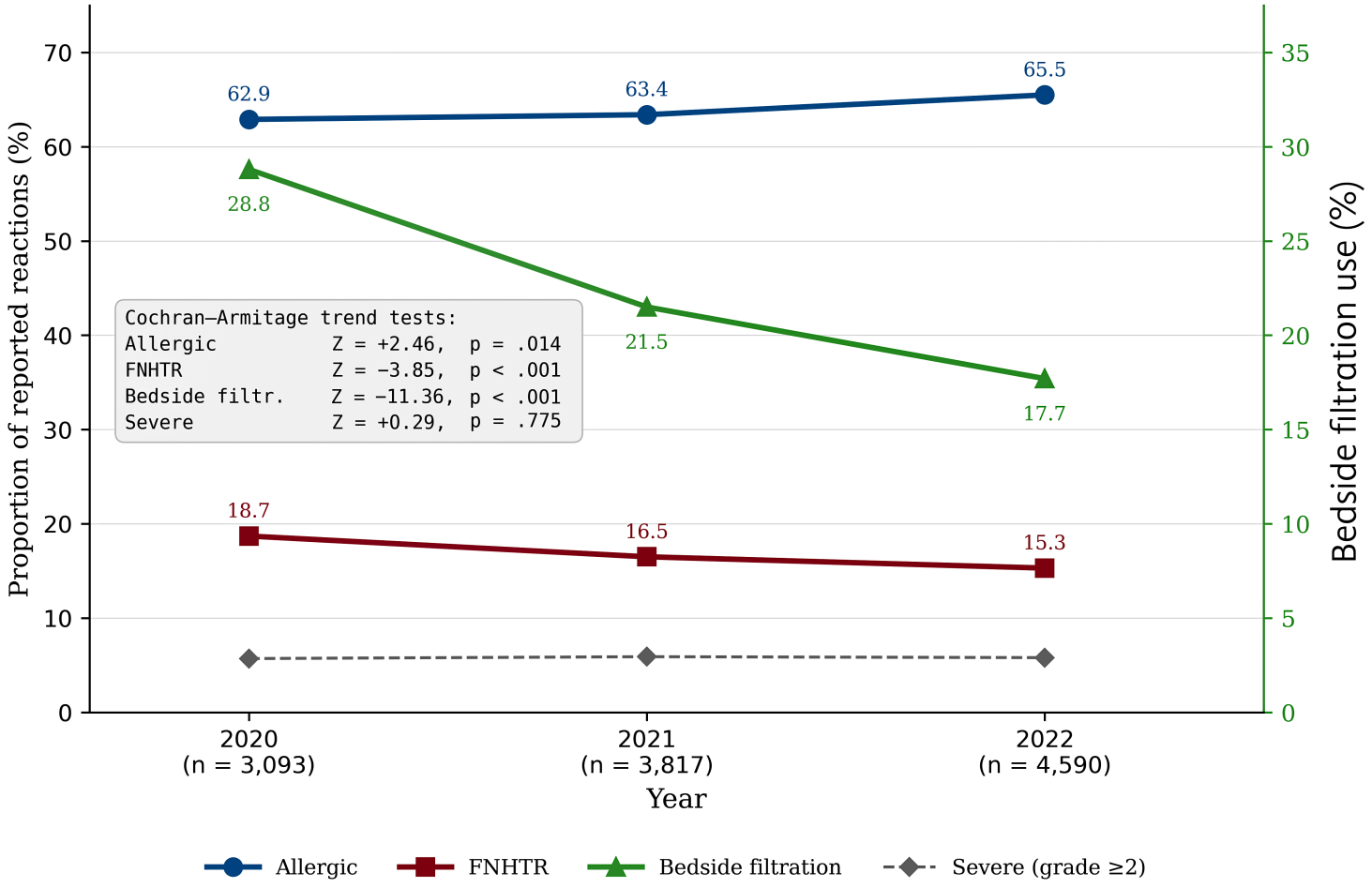


Figure 2

Temporal trends in allergic reactions, FNHTR, severe reactions (grade ≥2), and bedside filtration use among transfusion reaction reports in Türkiye, 2020–2022 (N = 11,500). Left y-axis: reaction-type proportions; right y-axis: bedside filtration use. Cochran–Armitage Z-statistics and p-values are shown. Allergic reactions increased modestly, FNHTR and bedside filtration declined, and the proportion of severe reactions remained stable over time.

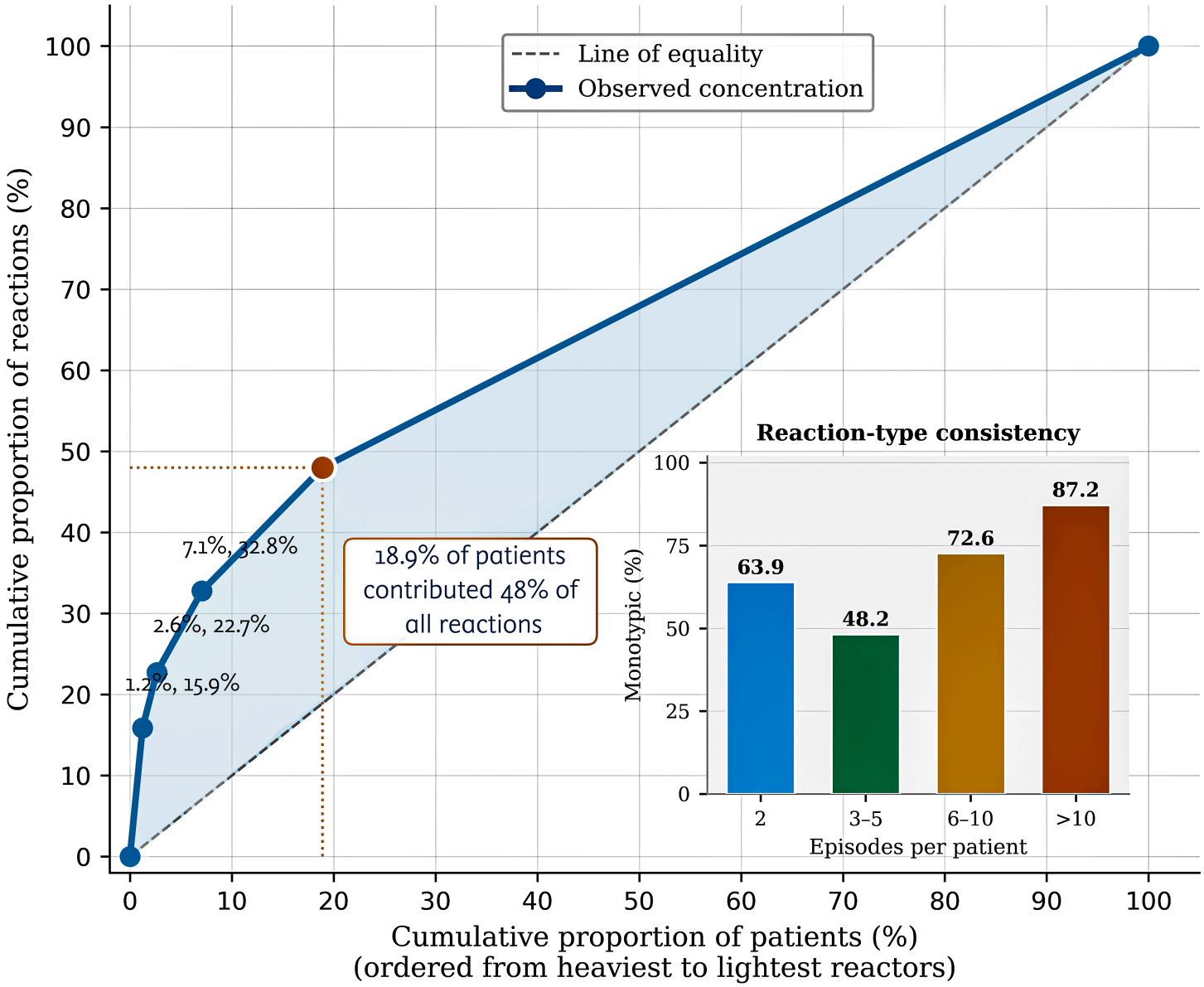


Figure 3

Concentration of the hemovigilance burden among repeat reactors. Main panel: Lorenz curve showing the cumulative proportion of reactions against the cumulative proportion of patients, ordered from heaviest to lightest reactors. The dashed diagonal represents perfect equality. The recurrence analysis was based on an extended matching frame of 11,858 analyzable reports and 7,608 estimated unique patients from the original registry extract, used to preserve within-patient recurrence histories. The highlighted point shows that 18.9% of patients in this extended recurrence-matching frame contributed 48.0% of its reports.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarytables.docx