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Evaluation of Thrombocytpenia in patients taking Antiepileptic Drugs: A Prospective Cohort Study

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Abstract

Background: Antiepileptic drugs (AEDs) are the foundation of epilepsy treatment, but hematological toxicity including thrombocytopenia is a frequent, and sometimes unrecognized, side effect, especially of valproic acid. The incidence and independent risk factors for this harmful effect in the south Asian tertiary care setting are still limited.

Objective: To examine the cumulative incidence and risk factors for AED-induced thrombocytopenia in treatment naive epileptic patients and primary hypothesis: To test the hypothesis that the use of valproic acid was independently associated with thrombocytopenia.

Methods: The prospective cohort study was carried out in Neurology and Haematology Department of a tertiary care hospital in Lahore, Pakistan for one year. A minimum of 195 participants was calculated to be needed using Cochran's formula and 196 adults with no prior use of AED who started on monotherapy (valproic acid, levetiracetam, carbamazepine or phenobarbital) were recruited for a study period of 24 weeks, with serial platelet counts. Independent predictors were determined by multivariable logistic regression, Cox proportional hazards regression and Kaplan-Meier survival analysis ($p<0.05$).

Results: The cumulative incidence of thrombocytopenia was 26.0% (51/196), and was highest with valproic acid (41.3%) compared with other AEDs combined (16.5%; relative risk 2.50, 95% CI 1.47–4.27, $p<0.001$). Mean platelet count declined significantly from 279.4±61.2×10⁹/L at baseline to 224.8±78.5×10⁹/L at week 24 (paired $t=9.42$, $p<0.001$). The use of valproic acid (adjusted OR 2.85, 95% CI 1.52–

5.34, p=0.001), higher dosage, longer duration of therapy, older age, polytherapy and lower baseline platelet count were all independent predictors of thrombocytopenia on multivariable logistic regression. Valproic acid had a significantly shorter time to onset (6 vs 12 weeks, log rank p=0.002).
Conclusions: AED-induced thrombocytopenia is frequent, especially when using valproic acid, and can be predicted from easily available clinical factors. To prevent bleeding problems, regular platelet counts should be performed and may be necessary during the initial 8–12 weeks of valproic acid treatment.

Introduction

Epilepsy is one of the most prevalent chronic neurological conditions in the world, with an estimated incidence of 50 million people [1,2] and with almost exclusive management based on long-term pharmacotherapy through the use of antiepileptic drugs (AEDs)1. The World Health Organization estimates that the burden of epilepsy in LMICs is disproportionately high3, with Pakistan accounting for almost 10% of the global epilepsy burden, as the prevalence of epilepsy in the country is around 9.99 per 10004,5. Prescribing of AEDs in Pakistani tertiary-care neurology services is large and lengthier in this scale. Notwithstanding their proven effectiveness, AEDs have been shown to have a wide range of side effects, including haematological toxicity (anaemia, leucopenia and thrombocytopenia) which is of clinical significance as it frequently occurs without symptoms; it can make people more likely to have serious bleeding [,6,7,8]. Thrombocytopenia has long been known to be induced by valproic acid, with a direct suppression of the bone-marrow, a reduction of platelet survival and immune-mediated destruction of platelets all contributing to this process, in a dose dependent fashion [3,4]; levetiracetam, carbamazepine and phenobarbital have been implicated from time to time at lesser and less consistent degrees [5,6]. But the current body of evidence consists primarily of individual case reports, small retrospective case series and descriptive audits of the occurrence of laboratory abnormalities without formal testing of factors associated with drug and patient level that independently predict thrombocytopenia, or describing the time course of development of thrombocytopenia [7,8]. However, the data from the Pakistani and wider South Asian tertiary care neurology practices are very limited, especially in light of the extensive prescription of valproic acid in this environment and the pharmacogenetic variations seen in Pakistani patients undergoing AED therapy [9] . This is a significant gap in the evidence: with no analytic and prospective quantification of risk, doctors will have no objective basis for determining which patients need closer monitoring of their platelet counts.

We therefore designed a prospective cohort study of AED-naïve newly diagnosed epilepsy patients to quantitate the cumulative incidence, time course and independent predictors of AED-induced thrombocytopenia. We a priori hypothesized that the risk of thrombocytopenia with VA therapy is significantly higher than other FLAEDs, regardless of age, sex, dose, duration of VA therapy, or baseline platelet count. Secondary aims were to (i) measure the platelet decline by drug group and over time; (ii) determine independent clinical and pharmacological factors associated with the development of thrombocytopenia by multivariable regression; and (iii) delineate the dose–response and duration–response relationships of platelet decline to AED exposure.

Methods

Study design
This was a hospital-based, analytical prospective cohort study conducted according to the STROBE guidelines for observational research.

Setting and duration
The study was conducted jointly in the Department of Neurology (outpatient and inpatient) and the Department of Haematology of a tertiary-care public-sector teaching hospital in Lahore, Pakistan. Recruitment took place over 12 months (January – December 2025); each enrolled participant was followed prospectively for 24 weeks from the date of AED initiation, giving a total study duration of approximately 18 months.

Study population
Inclusion criteria
Adults aged 18–65 years with newly diagnosed epilepsy (per International League Against Epilepsy criteria) requiring AED therapy for the first time (AED-naïve).
Initiation of monotherapy with one of the four study drugs: valproic acid, levetiracetam, carbamazepine or phenobarbital, at the treating neurologist's discretion.
Willingness to provide written informed consent and to attend scheduled follow-up visits for 24 weeks.

Exclusion criteria
Prior exposure to any AED.
Pre-existing haematological disorder (e.g., primary immune thrombocytopenia, myelodysplasia, leukaemia) or baseline platelet count $<150\times10^9$/L.
Chronic liver or renal disease, known bone-marrow-suppressive illness, or active infection (including HIV, hepatitis B/C) at enrolment.
Concurrent use of other medications known to affect platelet count or function (e.g., heparin, cytotoxic chemotherapy, co-trimoxazole, linezolid) or recent (<4 weeks) blood transfusion.
Pregnancy, or plan for AED polytherapy from the outset.
Incomplete baseline records or unwillingness to consent.

Sample size calculation
The minimum required sample size was calculated using Cochran's single-population proportion formula, appropriate for estimating an incidence proportion with a specified precision[26]:
$n = Z^2P(1-P) / d^2$
Z = 1.96 (standard normal deviate corresponding to a 95% confidence level)
P = 0.30 (anticipated proportion of AED-induced thrombocytopenia, based on the pooled range of 20–48% reported in prior studies)
d = 0.07 (absolute precision / margin of error)

Substituting these values: $n = (1.96)^2 \times 0.30 \times 0.70 / (0.07)^2 = 164.6$, rounded up to **165**. To account for an anticipated 15% loss to follow-up over the 24-week observation period, the minimum sample size was inflated as $n = 165 / (1 - 0.15) = 194.1$, rounded up to a required minimum of **195 participants**. A total of 246 consecutive patients were screened, of whom 210 met eligibility criteria and were enrolled; 14 (6.7%) were subsequently lost to follow-up or withdrew consent, leaving a final analytic cohort of **196 participants**, which exceeded the calculated minimum requirement (Figure 1).

Sampling technique
Consecutive (non-probability) sampling was used: all AED-naïve patients presenting to the Neurology outpatient/inpatient services who satisfied the eligibility criteria

during the recruitment window were invited to participate until the target sample size was achieved.

Data collection procedure

After written informed consent, a structured proforma was used to record demographic data (age, sex, weight, socio-economic status), seizure type and aetiology, comorbidities, and the AED prescribed with the starting and maintenance dose (mg/kg/day). A baseline venous blood sample for complete blood count, including platelet count, was drawn within 48 hours before initiation of AED therapy. Participants were then followed with repeat complete blood counts at 4, 8, 12, 16, 20 and 24 weeks, performed in the hospital's central Haematology laboratory using an automated haematology analyser with a standardised quality-control protocol. The date of onset of thrombocytopenia (first visit at which platelet count fell below 150×10^9/L) was recorded for time-to-event analysis. Serum AED concentration was measured at week 4 where clinically indicated to support therapeutic drug monitoring.

Study variables

Outcome variables

Primary outcome: development of thrombocytopenia (binary; yes/no) at any point during the 24-week follow-up.

Secondary outcomes: percentage decline in platelet count from baseline; time (weeks) to onset of thrombocytopenia.

Exposure and covariate variables

AED type (valproic acid, levetiracetam, carbamazepine, phenobarbital)

AED dose (mg/kg/day, continuous and categorised as high/low by drug-specific tertile)

Duration of therapy at each assessment (weeks)

Age (years), sex, body weight

Baseline platelet count ($\times10^9$/L)

Monotherapy vs. subsequent polytherapy (add-on AED during follow-up)

Operational definitions

Thrombocytopenia: platelet count $<150\times10^9$/L, graded per CTCAE v5.0 as mild ($100–149\times10^9$/L), moderate ($50–99\times10^9$/L) or severe ($<50\times10^9$/L). [27]

AED-naïve: no prior lifetime exposure to any antiepileptic or anticonvulsant medication.

Monotherapy: treatment with a single AED throughout the observation period; addition of a second agent was recorded as "polytherapy" from that time point onward.

High-dose subgroup: maintenance dose in the upper tertile of the drug-specific dose distribution in this cohort.

Time to onset: interval in weeks between AED initiation and the first documented platelet count $<150\times10^9$/L.

Statistical analysis plan

Data were entered in Microsoft Excel and analysed using IBM SPSS version 27.0, with survival analysis cross-checked in R version 4.3. Continuous variables were tested for normality using the Shapiro-Wilk test and are presented as mean±SD or median (IQR) as appropriate; categorical variables are presented as frequency (percentage).

Baseline platelet count vs. week-24 platelet count (whole cohort): paired-samples t-test (or Wilcoxon signed-rank test if non-normal).
Incidence of thrombocytopenia across the four drug groups: Chi-square test (Fisher's exact test where expected cell counts <5); relative risk with 95% CI for valproic acid vs. other AEDs combined.
Percentage platelet decline across drug groups: one-way ANOVA with Tukey's post-hoc test (or Kruskal-Wallis with Dunn's post-hoc test if non-normal).
Association between AED dose and percentage platelet decline: Pearson's or Spearman's correlation coefficient.
Independent predictors of thrombocytopenia (binary outcome): multivariable binary logistic regression, entering all covariates with $p<0.20$ on univariable analysis; results reported as adjusted odds ratios (aOR) with 95% CI. Model fit assessed with the Hosmer-Lemeshow test and Nagelkerke R^2.
Independent predictors of percentage platelet decline (continuous outcome): multivariable linear regression, reported as unstandardised regression coefficients (B) with 95% CI and model R^2.
Time to onset of thrombocytopenia: Kaplan-Meier survival curves compared with the log-rank test; multivariable Cox proportional-hazards regression to estimate adjusted hazard ratios (aHR) with 95% CI, with the proportional-hazards assumption checked using Schoenfeld residuals.
A two-tailed p-value <0.05 was considered statistically significant throughout.

Ethical approval and informed consent
The study protocol was approved by the Institutional Review Board / Ethical Review Committee of the hospital prior to recruitment (approval reference withheld for blinded review), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from every participant after a full explanation of the study's purpose, procedures, and the voluntary and confidential nature of participation; participants were free to withdraw at any stage without any effect on their clinical care. Patients who developed thrombocytopenia during follow-up were managed clinically (dose reduction, drug substitution, or haematology referral) independent of study participation.

Results
Participant flow and baseline characteristics
Of 246 patients screened, 210 met eligibility criteria and were enrolled; 14 (6.7%) were lost to follow-up or withdrew consent, leaving 196 participants (93.3%) who completed the full 24-week follow-up and were included in the final analysis (Figure The final sample exceeded the calculated minimum requirement of 195.

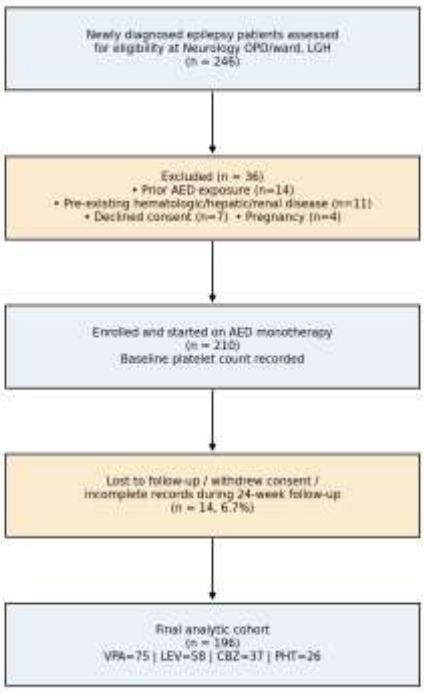

Figure 1. Participant flow diagram (STROBE format) from screening to final analytic cohort.

The mean age of the cohort was 32.4±10.8 years, and 118 (60.2%) were male. Valproic acid was the most frequently prescribed AED (75/196, 38.3%), followed by levetiracetam (58/196, 29.6%), carbamazepine (37/196, 18.9%) and phenobarbital (26/196, 13.3%). Baseline demographic, clinical and pharmacological characteristics were broadly comparable across the four drug groups (Table 1), with no statistically significant between-group differences in age, sex distribution or baseline platelet count (all $p>0.05$), supporting comparability of the groups at inception.

Table 1. Baseline demographic and clinical characteristics of the study cohort, overall and by antiepileptic drug (AED) group (N=196).

Characteristic	Overall (N=196)	Valproic acid (n=75)	Levetiracetam (n=58)	Carbamazepine (n=37)	Phenobarbital (n=26)
Age, years, mean±SD	32.4±10.8	33.1±11.2	31.0±10.1	32.8±10.6	32.9±11.0
Male sex, n (%)	118 (60.2)	44 (58.7)	36 (62.1)	23 (62.2)	15 (57.7)
Body weight, kg, mean±SD	62.7±11.4	63.5±12.0	61.8±10.9	62.1±11.5	63.0±11.8
Generalised tonic-clonic seizures, n (%)	141 (71.9)	58 (77.3)	39 (67.2)	26 (70.3)	18 (69.2)
Focal seizures, n (%)	55 (28.1)	17 (22.7)	19 (32.8)	11 (29.7)	8 (30.8)
AED dose, mg/kg/day,	—	18.4±4.7	22.6±5.9	12.1±3.2	3.8±1.1

mean±SD					
Baseline platelet count, ×10⁹/L, mean±SD	279.4±61.2	283.6±58.9	276.5±63.7	274.1±59.8	281.9±64.4
Polytherapy added during follow-up, n (%)	34 (17.3)	16 (21.3)	9 (15.5)	5 (13.5)	4 (15.4)

Values are mean±SD or n (%) unless otherwise indicated. AED = antiepileptic drug.

Cumulative incidence of thrombocytopenia

Over the 24-week follow-up, 51 of 196 participants (26.0%, 95% CI 19.9–32.1%) developed thrombocytopenia. Incidence differed significantly across the four AED groups (χ^2=11.82, df=3, p=0.008), and was highest with valproic acid (31/75, 41.3%) compared with levetiracetam (12/58, 20.7%), phenobarbital (4/26, 15.4%) and carbamazepine (4/37, 10.8%) (Table 2, Figure 2). Patients receiving valproic acid had a 2.50-fold higher risk of developing thrombocytopenia than those receiving any other AED (relative risk 2.50, 95% CI 1.47–4.27, p<0.001).

Table 2. Cumulative incidence of thrombocytopenia by antiepileptic drug group.

AED group	N	Thrombocytopenia, n (%)	95% CI	Relative risk (vs. other AEDs)
Valproic acid	75	31 (41.3%)	30.2–52.5%	2.50 (1.47–4.27)
Levetiracetam	58	12 (20.7%)	10.3–31.1%	Reference
Carbamazepine	37	4 (10.8%)	0.8–20.8%	Reference
Phenobarbital	26	4 (15.4%)	1.5–29.3%	Reference
Overall cohort	196	51 (26.0%)	19.9–32.1%	—

Relative risk calculated for valproic acid versus the pooled group of other three AEDs (16.5% incidence); χ^2=11.82, df=3, p=0.008 for overall between-group comparison.

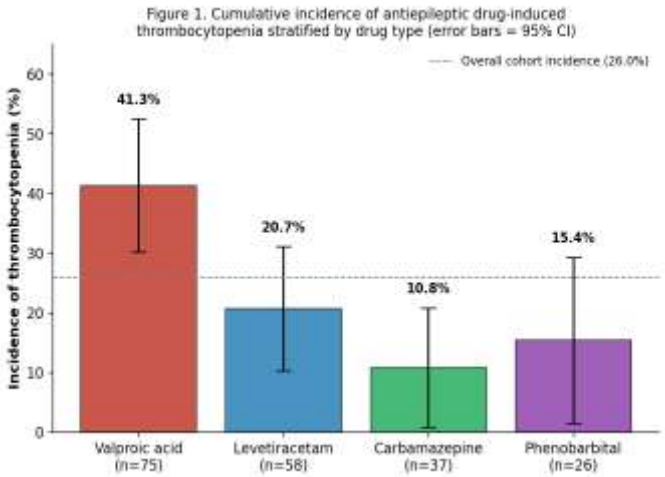

Figure 2. Cumulative incidence (%) of antiepileptic drug-induced thrombocytopenia stratified by drug type. Error bars represent 95% confidence intervals; dashed line indicates the overall cohort incidence.

Change in platelet count following AED therapy

Across the whole cohort, mean platelet count fell significantly from 279.4±61.2×10⁹/L at baseline to 224.8±78.5×10⁹/L at week 24 (paired t=9.42, df=195, p<0.001; mean decline 54.6×10⁹/L, 95% CI 43.1–66.1). The magnitude of decline differed significantly by drug group on one-way ANOVA (F=14.87, df=3,192, p<0.001); Tukey's post-hoc test confirmed that the valproic acid group had a significantly greater decline than each of the other three groups (all p<0.05), and that levetiracetam differed significantly from carbamazepine (p=0.048) but not from phenobarbital (p=0.21) (Table 3, Figure 3).

Table 3. Pre- and post-therapy platelet counts by antiepileptic drug group.

AED group	Baseline platelet ×10⁹/L, mean±SD	Week-24 platelet ×10⁹/L, mean±SD	Mean decline (95% CI)	p-value*
Valproic acid	283.6±58.9	189.2±71.4	94.4 (79.6–109.2)	<0.001
Levetiracetam	276.5±63.7	238.9±69.5	37.6 (24.1–51.1)	<0.001
Carbamazepine	274.1±59.8	251.3±58.2	22.8 (7.2–38.4)	0.006
Phenobarbital	281.9±64.4	248.7±61.0	33.2 (9.6–56.8)	0.008
Overall cohort	279.4±61.2	224.8±78.5	54.6 (43.1–66.1)	<0.001

**Paired-samples t-test comparing baseline and week-24 platelet count within each group.*

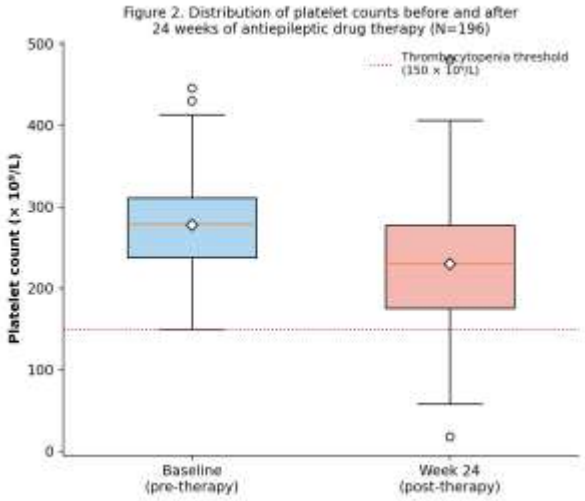

Figure 3. Distribution of platelet counts at baseline and week 24 for the overall cohort (N=196). The horizontal dotted line marks the thrombocytopenia threshold (150×10⁹/L).

Within the valproic acid group, AED dose (mg/kg/day) correlated positively with the percentage decline in platelet count (Spearman's ρ=0.46, p<0.001), indicating a dose-dependent relationship.

Independent predictors of thrombocytopenia — multivariable logistic regression
On multivariable binary logistic regression (Table 4), valproic acid use remained an independent predictor of thrombocytopenia after adjustment for age, sex, baseline platelet count, dose, duration of therapy and polytherapy status (adjusted OR 2.85, 95% CI 1.52–5.34, p=0.001). Older age, higher dose, longer duration of therapy (>12 weeks), and polytherapy were each independently associated with increased odds of thrombocytopenia, whereas a higher baseline platelet count was protective. Female sex showed a trend toward higher risk that did not reach statistical significance. The model showed good fit (Hosmer-Lemeshow p=0.62), explained 28.4% of the variance in outcome (Nagelkerke R^2=0.284), and correctly classified 78.7% of cases (overall model χ^2=42.6, df=7, p<0.001).

Table 4. Multivariable logistic regression for independent predictors of thrombocytopenia.

Predictor	Adjusted OR	95% CI	p-value
Valproic acid (vs. other AEDs)	2.85	1.52–5.34	0.001
Age (per 10-year increase)	1.32	1.05–1.66	0.017
Female sex	1.68	0.92–3.07	0.092
Baseline platelet count (per 50×10⁹/L increase)	0.71	0.55–0.92	0.009
High-dose subgroup (upper tertile)	2.10	1.12–3.94	0.021
Duration of therapy >12 weeks	1.95	1.03–3.69	0.041
Polytherapy (vs. monotherapy)	2.34	1.18–4.64	0.015

Model: Hosmer-Lemeshow p=0.62; Nagelkerke R^2=0.284; overall model χ^2=42.6, df=7, p<0.001; classification accuracy 78.7%.

Predictors of magnitude of platelet decline — multivariable linear regression
Multivariable linear regression for percentage platelet decline (Table 5) confirmed valproic acid use, higher dose, longer duration of therapy, older age and polytherapy as independent predictors of a greater decline, while a higher baseline platelet count was associated with a smaller percentage decline. The overall model explained 38.6% of the variance in percentage platelet decline (R^2=0.386, adjusted R^2=0.366, F=18.94, df=6,181, p<0.001).

Table 5. Multivariable linear regression for predictors of percentage platelet decline.

Predictor	B (unstd.)	95% CI	p-value
Valproic acid (vs. other AEDs)	18.4	12.1–24.7	<0.001
Dose (per 10 mg/kg/day)	1.85	1.02–2.68	<0.001
Duration of therapy (per week)	0.38	0.11–0.65	0.006
Age (per year)	0.21	0.05–0.37	0.011

Baseline platelet count (per 10×10⁹/L)	-0.09	-0.15 to -0.03	0.004
Polytherapy (vs. monotherapy)	6.72	1.15–12.29	0.018

Model: R^2=0.386, adjusted R^2=0.366; F=18.94, df=6,181, p<0.001.

Time to onset of thrombocytopenia

Among the 51 participants who developed thrombocytopenia, the median time to onset was 8 weeks (IQR 6–14). Time to onset was significantly shorter in the valproic acid group (median 6 weeks, IQR 4–10) than in the pooled other-AED group (median 12 weeks, IQR 8–16); Kaplan-Meier estimates diverged early and were significantly different by the log-rank test (χ^2=9.87, df=1, p=0.002) (Figure 4). On multivariable Cox proportional-hazards regression (Table 6), valproic acid use remained independently associated with earlier onset of thrombocytopenia (adjusted HR 2.41, 95% CI 1.28–4.54, p=0.006), as did older age and polytherapy, while higher baseline platelet count was protective. The proportional-hazards assumption was not violated for any covariate (Schoenfeld residual p>0.05 for all).

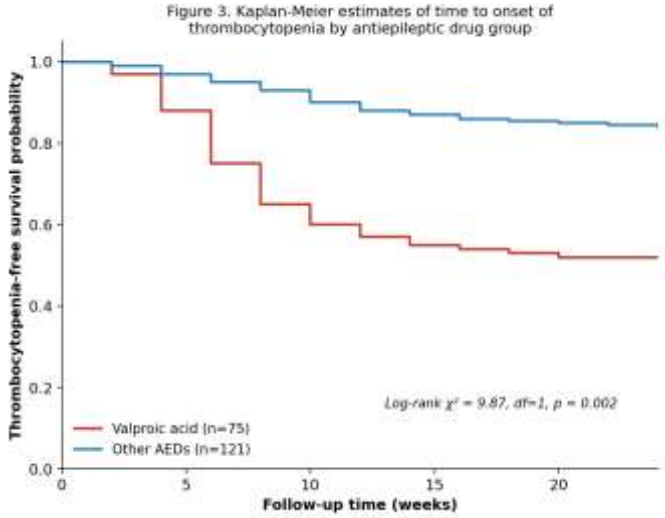

Figure 4. Kaplan-Meier estimates of thrombocytopenia-free survival by antiepileptic drug group over 24 weeks of follow-up.

Table 6. Multivariable Cox proportional-hazards regression for time to onset of thrombocytopenia.

Predictor	Adjusted HR	95% CI	p-value
Valproic acid (vs. other AEDs)	2.41	1.28–4.54	0.006
Baseline platelet count (per 50×10⁹/L)	0.68	0.51–0.90	0.007
Age (per 10-year increase)	1.24	1.02–1.51	0.031
Polytherapy (vs. monotherapy)	1.87	1.01–3.46	0.046

Proportional-hazards assumption confirmed by Schoenfeld residuals (p>0.05 for all covariates).

Discussion

Principal findings

In this prospective cohort of 196 AED-naïve patients with newly diagnosed epilepsy, more than one in four (26.0%) developed thrombocytopenia within 24 weeks of starting therapy. Consistent with our primary hypothesis, valproic acid was associated with both a substantially higher cumulative incidence (41.3% vs. 16.5% for other AEDs; relative risk 2.50) and a markedly shorter time to onset (median 6 vs. 12 weeks) of thrombocytopenia. This association persisted after multivariable adjustment for age, sex, dose, duration of therapy, baseline platelet count and polytherapy in three independent analytic frameworks — logistic regression (adjusted OR 2.85), linear regression of percentage decline (B=18.4), and Cox regression of time to onset (adjusted HR 2.41) — providing convergent evidence that the valproic acid–thrombocytopenia association in this cohort is unlikely to be explained by confounding from the measured covariates alone.

Comparison with previous studies

Our incidence estimate for valproic acid (41.3%) sits within, albeit toward the upper end of, the wide range of 5–60% previously reported for valproate-associated thrombocytopenia[9], and is comparable with the prospective monotherapy study of Nasreddine and Beydoun, who similarly identified dose and duration as key correlates of platelet decline[11]. The lower incidence observed with levetiracetam, carbamazepine and phenobarbital in our cohort mirrors the case-report-dominated literature for these agents, in which thrombocytopenia is described as an uncommon but clinically significant idiosyncratic reaction rather than a frequent, dose-related phenomenon[12,13,14,15,16]. Our finding of a reduction in complete blood count parameters, including platelet count, following AED therapy is concordant with the retrospective series of Kırar et al.[17], and with paediatric data documenting anaemia, leucopenia and thrombocytopenia during AED treatment[18]. Taken together with the pharmacogenetic variability previously documented among Pakistani patients receiving valproic acid and carbamazepine[21], our results extend the evidence base by providing, to our knowledge, one of the first analytic, prospective quantifications of incidence, dose-response and time-to-event relationships for AED-induced thrombocytopenia in a South Asian tertiary-care population.

Biological and clinical mechanisms

The mechanisms underlying valproic acid-induced thrombocytopenia are considered multifactorial: direct, dose-dependent suppression of megakaryopoiesis in the bone marrow, shortened peripheral platelet survival, and incorporation of the drug into the platelet membrane with consequent generation of anti-platelet autoantibodies and immune-mediated platelet destruction[9,10,11]. This dual toxic and immune mechanism plausibly explains both the dose-response relationship demonstrated in our cohort (positive correlation between dose and percentage decline) and the earlier onset relative to other AEDs, since direct marrow suppression would be expected to manifest sooner than antibody-mediated peripheral destruction alone. For levetiracetam, carbamazepine and phenobarbital, the literature more consistently favours an idiosyncratic, non-dose-dependent, immune-mediated hypersensitivity mechanism, often accompanied by other cytopenias [12,13,15,16], which is compatible with the flatter dose-response and later, more variable onset observed for these agents in our data. Older age and lower baseline platelet count were independent predictors across all three regression models, plausibly reflecting reduced bone-marrow reserve and a smaller physiological buffer before crossing the diagnostic threshold for thrombocytopenia, respectively; the independent contribution of polytherapy is consistent with additive or synergistic marrow-suppressive or immune-mediated effects when a second AED is introduced.

Strengths

This study has several strengths. First, the prospective, AED-naïve cohort design with a pre-specified sample size and pre-defined hypothesis allowed genuine analytic inference rather than purely descriptive reporting, avoiding the reverse-causation and recall bias inherent in retrospective case series. Second, serial platelet counts at fixed intervals allowed formal time-to-event analysis (Kaplan-Meier, Cox regression) in addition to the more commonly reported pre-post comparison, characterising both the magnitude and timing of the effect. Third, the use of three complementary multivariable regression models (logistic, linear, Cox) converging on the same independent predictors substantially strengthens confidence in the robustness of the valproic acid association. Finally, the study was conducted according to STROBE reporting recommendations [22] with a priori operational definitions and a pre-registered statistical analysis plan.

Limitations

Several limitations warrant consideration. This was a single-centre study, which may limit generalisability to other populations and prescribing patterns. Non-probability consecutive sampling, while pragmatic, could introduce selection bias if referral patterns to this tertiary centre differ systematically from community practice. The 24-week observation window, although adequate to capture the majority of early-onset thrombocytopenia, cannot exclude later-onset events; longer follow-up would be required to characterise the full time course. Serum AED concentrations were not measured at every visit, limiting our ability to fully separate the effects of prescribed dose from actual drug exposure. Finally, although the multivariable models adjusted for the major measured confounders, residual confounding from unmeasured factors such as nutritional status, concurrent viral infection, or genetic polymorphisms in drug metabolism cannot be entirely excluded.

Implications and recommendations

These findings support the routine incorporation of platelet-count monitoring into the first 8–12 weeks of valproic acid therapy, particularly in patients who are older, are started on higher doses, or are subsequently escalated to polytherapy, since this is the period during which the majority of cases became apparent in our cohort. Baseline platelet count should be documented before starting therapy in all patients, both to satisfy exclusion criteria for pre-existing cytopenia and to allow individualised risk stratification using the predictive factors identified here. Therapeutic drug monitoring, where available, may allow individualised dose titration and further mitigate dose-related haematological toxicity[19,20]. Future multicentre studies with longer follow-up, inclusion of paediatric populations, and incorporation of serum drug-level monitoring at every visit are recommended to validate and refine a clinically usable risk-prediction model for AED-induced thrombocytopenia.

Conclusion

In this prospective cohort study from a tertiary-care hospital in Lahore, Pakistan, antiepileptic drug therapy — particularly valproic acid — was associated with a clinically significant and independently predictable risk of thrombocytopenia, occurring earliest and most frequently with valproic acid and increasing with higher dose, longer duration of therapy, older age, polytherapy and lower baseline platelet count. These findings confirm our primary hypothesis and support routine, risk-stratified platelet-count monitoring, especially during the first 8–12 weeks of valproic acid therapy, to enable early detection and timely dose adjustment or drug substitution before clinically significant bleeding occurs.

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