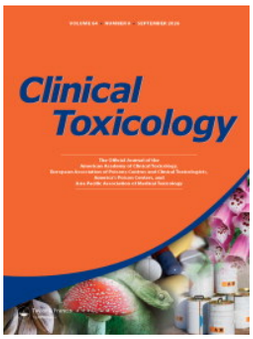

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Predicting SILENT after lithium poisoning: a multicenter cohort study and pragmatic risk stratification model

Álvaro Pineda-Torcuato[a,b], Antonio F. Caballero-Bermejo[a,c], August Supervia[d,e,f], Emilio Salgado[g], Ruadhan O'Laoi[h,i], Carolina Sánchez[g], Francisca Córdoba[j], Neus Rodríguez Farré[k], Natalia Sanz-López[l], Héctor Hernández Ontiveros[l], Blanca Andrea Gallardo Sánchez[m], Paula Romero Gallardo[m], Victoria Lobo-Antuña[n], Benjamín Climent[n], Sandra Mora Azabal[o], Alberto Cózar-Llistó[p], Marina Vergara Ortiz[p], Mikel Urroz-Elizalde[q], Valle Molina Samper[r], Pablo Navarro Román[d,e], Xavier Canseco Suárez[s], Francisco J. Callado Moro[t], Cormack Kennedy[h,i], María del Pilar Gómez Jiménez[u], M. Àngels Gispert-Ametller[v], Macarena Lucila Míguez del Águila[v], Isabel Llopis Sanmillán[w], Luca Cioccari[w,x], Beatriz Martín Pérez[y], Susanna Vert García[z], Andrea Terron Sánchez[aa], Guillermo Burillo-Putze[ab,ac], Edith Gutiérrez[ad], Santiago Nogué-Xarau[ae,af], Jordi Puiguriguer-Ferrando[ag] and Belén Ruiz-Antorán[a,c]

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ABSTRACT

Introduction: The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) is a rare but potentially devastating complication of lithium poisoning. Current evidence rests on case reports and small series, leaving its true incidence, risk factors, and follow-up tools poorly defined.
Methods: Retrospective, international, multicenter cohort of adults evaluated for lithium poisoning (2015–2022) across 23 tertiary hospitals in Spain, Ireland, and Switzerland. SILENT was defined as persistent neurological sequelae attributed to lithium toxicity documented at 60 days. A parsimonious multivariable logistic regression model was built from routinely available clinical variables and assessed by ROC analysis and internal split-sample validation.
Results: Among 644 episodes, SILENT was identified in 49 (7.6%); predicted probabilities were available for 456 episodes (39 SILENT cases). Affected patients were older and more often had acute-on-chronic poisoning, early neurological manifestations, and greater clinical severity. Serum lithium concentrations were not associated with SILENT. The model—age, poisoning type, neurological findings (ataxia/myoclonus), Poisoning Severity Score, and peak urea—showed good discrimination (AUC 0.813; 95% CI 0.743–0.882) and acceptable internal validation (AUC 0.730; 95% CI 0.572–0.888). A sensitivity-oriented threshold (P≥0.0475) yielded a high negative predictive value (98.2%), supporting its use to prioritize post-discharge neurological follow-up.

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Discussion: SILENT occurred more frequently than case-based literature suggests and followed a recognizable presentation pattern. Serum lithium alone did not predict long-term sequelae. The model, based on routine variables, may offer a pragmatic tool for early risk stratification.
Conclusion: SILENT is not an exceptional outcome after lithium poisoning and cannot be predicted by serum lithium alone. A simple clinical prediction model may identify patients warranting structured neurological follow-up. External validation is required before implementation.

Introduction

Lithium is a cornerstone mood stabilizer used in the treatment of bipolar disorder and other psychiatric conditions [1]. Despite its well-established efficacy, its clinical use is limited by a narrow therapeutic index, with toxic serum concentrations (≥1.5 mmol/L) occurring close to therapeutic levels (0.8–1.2 mmol/L for acute episodes and 0.8–1.0 mmol/L for maintenance therapy) [2]. As a result, lithium poisoning remains a frequent cause of emergency department presentation [3,4] particularly in patients with renal impairment, dehydration, drug–drug interactions, or intercurrent illnesses. Clinically, lithium poisoning is classified as acute, chronic, or acute-on-chronic, with chronic and acute-on-chronic exposures carrying a higher risk of neurological toxicity [5]. Neurological manifestations range from mild tremor and ataxia to confusion, seizures, coma, and irreversible brain injury [6]. Management consists of lithium discontinuation, supportive care, and, in severe cases, extracorporeal renal replacement therapy (RRT) [5,7,8].

the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) is a rare but severe complication of lithium poisoning, characterized by the persistence of neurological deficits despite lithium discontinuation and appropriate management of the acute episode [9]. The syndrome is classically dominated by cerebellar dysfunction—such as ataxia, nystagmus, dysarthria, and gait disturbances—that persists for at least two months after the acute episode [10–12]. Although uncommon, with relatively few cases reported in the literature, SILENT most often occurs during routine lithium therapy rather than after acute overdose. Notably, it may develop even at therapeutic or mildly elevated lithium concentrations and after apparent clinical recovery [13,14]. Advanced age, renal impairment, intercurrent infections or fever, and concomitant antipsychotic use have been consistently identified as predisposing factors [9]. These features highlight SILENT as an infrequent yet potentially devastating outcome of lithium toxicity, underscoring the difficulty of early recognition and prevention. However, its definition remains uncertain, largely due to its heterogeneous clinical presentation [15], incomplete understanding of the underlying pathophysiology [9], and occurrence across a wide range of lithium concentrations, including therapeutic levels. The absence of consistent clinical or biochemical thresholds, reliance on an arbitrary time-based criterion, and the rarity of the condition—mostly described in retrospective reports—have hindered the development of a standardized definition in clinical practice.

Most patients with lithium poisoning are discharged without clear criteria for neurological follow-up, as standardized post-discharge protocols and specific guidelines for lithium-related neurotoxicity are lacking, and the definition of SILENT remains largely operational and poorly standardized [16]. Consequently, SILENT is often diagnosed late, when neurological damage is already irreversible, as cerebellar and other deficits may emerge or persist weeks after the acute episode and correlate poorly with serum lithium concentrations. The absence of specific biomarkers, the limited sensitivity of conventional neuroimaging in early stages, and insufficient clinical awareness further hinder early identification [17]. Overall, there is a critical unmet need for simple, validated tools based on routinely available clinical variables to identify patients at risk and guide structured neurological follow-up after discharge.

The aim of this study is to characterize the frequency and clinical spectrum of SILENT in a large, international, multicenter cohort of lithium poisoning episodes, to identify factors associated with its development, and to develop and internally validate a pragmatic prediction model based on routinely available clinical variables to support early post-discharge risk stratification.

Methods

Study design and population

This retrospective, observational, international multicenter study included all eligible episodes of lithium poisoning managed between 2015 and 2022 in the Emergency Departments and/or Clinical Toxicology

Units of 23 tertiary hospitals in Spain, Ireland, and Switzerland. Cases were identified retrospectively from local clinical records and registries. Data were abstracted from the electronic medical record and entered into a pseudoanonymized study database. Clinical records were reviewed for up to 60 days after the index episode.

We included adult patients (≥18 years) evaluated for lithium poisoning, defined by a compatible clinical context (history of lithium exposure/ingestion and/or clinical toxicity) together with elevated serum lithium concentrations, with or without symptoms. The study was restricted to adults to maintain a clinically homogeneous cohort, as pediatric lithium exposures often represent a different clinical scenario. Episodes were classified as acute, acute-on-chronic, or chronic using definitions consistent with prior literature and published studies [7,18]. Episodes with insufficient information to characterize the poisoning episode and/or to ascertain outcomes were excluded.

The study was approved by a Research Ethics Committee for Medicinal Products (CEIm) in each participating country and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The ethics committees waived the requirement for informed consent. The study was registered on 13 February 2023 in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (EUPAS 103542).

Data collection and outcome definition

For each episode, we collected demographics (age, sex), relevant comorbidities, and concomitant treatments when documented, as well as characteristics of the poisoning episode (type, presumed cause, co-ingestions, and potential precipitating factors). Clinical manifestations were recorded, including neurologic, gastrointestinal, cardiovascular, and renal features. Laboratory data included serum lithium concentrations (initial and peak values when available) and other routinely collected biochemical parameters during the clinical course (eg, creatinine, urea, electrolytes, and acid–base variables), as documented in the medical record. Clinical severity was assessed using the Poisoning Severity Score when available.

In addition, all episodes were retrospectively reviewed on a case-by-case basis and adjudicated according to EXTRIP criteria as renal replacement therapy (RRT) recommended, suggested, or not recommended, regardless of whether RRT was actually performed.

The primary outcome was SILENT (yes/no) at 60 days, defined as persistent neurologic sequelae attributed to lithium toxicity documented in the medical record, consistent with published descriptions of SILENT, including cerebellar dysfunction (eg, ataxia) or other recognized persistent neurologic sequelae (eg, extrapyramidal syndromes, brainstem dysfunction, or cognitive impairment) [15]. Outcome ascertainment was based on review of the electronic medical record.

Statistical analysis

Continuous variables are presented as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate, and categorical variables as counts and percentages. Group comparisons between SILENT and non-SILENT episodes were performed using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. The unit of analysis was the poisoning episode; episodes were analyzed independently, and no clustering by patient was applied.

A parsimonious multivariable prediction model was developed to estimate the probability of SILENT at 60 days (binary outcome), prioritizing clinical usability at discharge and minimizing model instability due to interrelated candidate variables. The final multivariable binary logistic regression model included the following prespecified predictors: age (years), poisoning type (acute/acute-on-chronic/chronic), ataxia (yes/no), myoclonic jerks (yes/no), moderate-to-severe poisoning (Poisoning Severity Score [PSS] ≥ 2; yes/no), and peak urea during the acute course (mmol/L). Poisoning type was modeled as a three-level categorical variable using two dummy variables with acute poisoning as the reference category. Individual predicted probabilities were computed from the fitted regression equation (intercept and coefficients). The full regression equation, variable coding, and an Excel-based risk calculator (SILENT-60 Risk Calculator, derived from the SILITOX study) to estimate the predicted probability of SILENT at 60 days are provided in Supplementary Table S4, and the Excel calculator as Supplementary File S1.

Model discrimination was assessed using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) with 95% confidence interval. Given the intended use as a screening tool to minimize missed cases, a probability threshold prioritizing sensitivity was selected based on ROC curve coordinates; the selected threshold value and its diagnostic performance (sensitivity, specificity, positive predictive value, and

negative predictive value) are reported in the Results section.

Model calibration was assessed by comparing observed and predicted SILENT risk across deciles of predicted probability among episodes with complete predictor data; the calibration table is provided in the (Supplementary Material Table S5; complete-case analysis).

Internal validation was performed using a random split-sample approach (70% derivation, 30% validation). Model discrimination and threshold-based performance were assessed in the validation subset using predicted probabilities computed from the final regression equation. Predicted probabilities could be computed in 456 episodes; therefore, model performance was evaluated in complete cases, as probabilities could not be estimated in 188 episodes due to missing data in one or more covariates. No multiple imputation was performed, and the model is intended for use only when all predictors are available at discharge. All analyses were performed using IBM SPSS Statistics for Windows (version 26.0; IBM Corp., Armonk, NY, USA). This study is reported in accordance with the STROBE statement and the TRIPOD statement for prediction model reporting.

Results

Study population and baseline characteristics

A total of 644 lithium poisoning episodes were included (Figure 1). The SILENT at 60 days was identified in 49/644 (7.6%) episodes.

Baseline characteristics and key clinical and laboratory findings by SILENT status are summarized in Table 1; the full set of variables is provided in Supplementary Table S1. Episodes that developed SILENT involved older patients (median age 67 vs 60 years; $P<0.001$). Pre-existing neurological comorbidities were present in 10/49 (20.4%) SILENT episodes and 81/595 (13.6%) in non-SILENT episodes ($P=0.189$). Pre-existing renal impairment was more common among SILENT episodes (chronic kidney disease stage ≥2: 20.4% vs 7.2%; $P=0.001$).

The distribution of poisoning type differed between groups ($P=0.003$), with a higher proportion of acute-on-chronic episodes among SILENT cases (51.0% vs 28.7%).

The presumed cause also differed, with fewer suicidal exposures among SILENT cases (8.2% vs 24.0%; $P=0.004$). Co-ingestion of other drugs was less frequent in SILENT (6.1% vs 22.0%; $P=0.024$). Neurologic manifestations during the index episode were more frequent in SILENT cases (98.0% vs 78.8%; $P=0.001$), and overall clinical severity was greater, with a higher proportion of cases graded as moderate-to-severe poisoning (PSS ≥2: 75.5% vs 43.2%; $P<0.001$).

Regarding management, RRT was used in 134/644 (20.8%) episodes and did not differ between SILENT and non-SILENT episodes. In exploratory analyses, neither receipt of RRT nor EXTRIP adherence was significantly associated with SILENT at 60 days. Among the 49 episodes that met the definition of SILENT, 37 did not receive RRT; of these, six retrospectively fulfilled EXTRIP-recommended criteria, 16 fulfilled EXTRIP-suggested criteria, and 15 did not meet EXTRIP criteria.

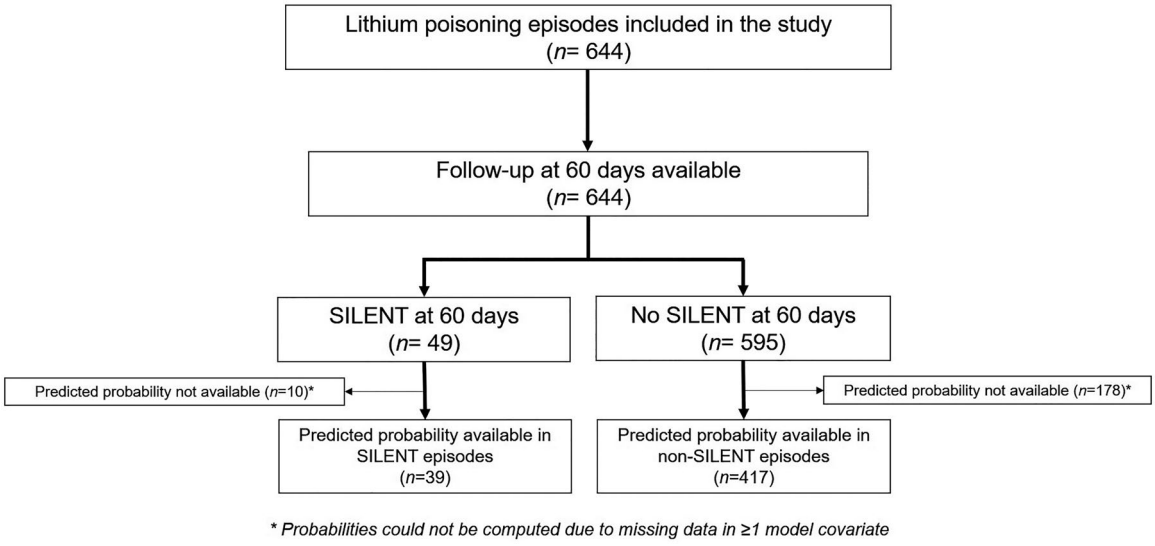

Figure 1. Flowchart of the study population, including lithium poisoning episodes, availability of 60-day follow-up, and SILENT outcomes. Predicted probabilities could not be computed in some episodes due to missing data in one or more model covariates.

Table 1. Baseline characteristics of the study cohort by SILENT status at 60 days.

Variable	SILENT ($n=49$)	No SILENT ($n=595$)	Total ($n=644$)	P
Sex – female, *n* (%)	31 (63.3)	377 (63.4)	408 (63.4)	0.989
Age, years, median (IQR)	67 (62.5–74.5)	60 (50–70)	61 (51–70)	<0.001
Comorbidities, *n* (%)				
Chronic kidney disease (CKD) stage ≥2	10 (20.4)	43 (7.2)	53 (8.2)	0.001
Cardiovascular comorbidities	4 (8.2)	42 (7.1)	46 (7.1)	0.773
Neurological comorbidities	10 (20.4)	81 (13.6)	91 (14.1)	0.189
Type of poisoning, *n* (%)				0.003
Acute	5 (10.2)	131 (22.0)	136 (21.1)	
Acute-on-chronic	25 (51.0)	171 (28.7)	196 (30.4)	
Chronic	19 (38.8)	293 (49.2)	312 (48.4)	
Co-ingestion of other drugs/substances, *n* (%)	3 (6.1)	131 (22.0)	134 (20.8)	0.024
Laboratory findings, mean (*SD*)				
Initial lithium concentration (mmol/L)	2.16 (0.70)	2.18 (1.01)	2.17 (0.99)	0.933
Peak lithium concentration (mmol/L)	2.17 (0.84)	2.37 (1.12)	2.35 (1.10)	0.224
Initial creatinine (µmol/L)	155.58 (103.44)	122.90 (80.44)	124.64 (82.25)	0.007
Peak creatinine (µmol/L)	166.19 (109.62)	129.95 (84.86)	132.60 (104.35)	0.006
Initial urea (mmol/L)	26.20 (15.09)	17.95 (13.54)	19.23 (16.88)	<0.001
Peak urea (mmol/L)	31.65 (33.59)	18.80 (14.11)	19.43 (14.33)	0.002
Any symptoms, *n* (%)	49 (100)	521 (87.6)	570 (88.5)	0.032
Gastrointestinal symptoms	20 (40.8)	208 (35.0)	228 (35.4)	0.410
Neurological symptoms	48 (98.0)	469 (78.8)	517 (80.3)	0.001
Cardiovascular symptoms	10 (20.4)	64 (10.8)	74 (11.5)	0.042
Poisoning Severity Score (PSS) ≥2, n (%)	37 (75.5)	256 (43.2)	293 (45.6)	<0.001

Notes: To convert urea from mmol/L to mg/dL, multiply by 2.801; to convert creatinine from µmol/L to mg/dL, divide by 88.4. SD, standard deviation; IQR, interquartile range; PSS, Poisoning Severity Score.

Therefore, 22/37 (59.5%) of SILENT episodes without RRT retrospectively fulfilled at least suggested or recommended EXTRIP criteria. Patients who developed SILENT were more frequently admitted to the intensive care unit (22.4% vs 15.6%; $P=0.003$); however, the median ICU length of stay was similar (4 [IQR 2–10] vs 5 [IQR 2–11] days; $P=0.972$). All-cause mortality at 60 days was low (22/644 [3.4%]) and did not differ between groups ($P=0.790$).

Clinical characterization of the syndrome of irreversible lithium-effectuated neurotoxicity

The neurological clinical manifestations documented at 60 days among patients meeting the definition of SILENT (n = 49) are summarized in Table 2. The most frequent manifestations were extrapyramidal symptoms (20/49, 40.8%), cognitive impairment (14/49, 28.6%), and cerebellar dysfunction (12/49, 24.5%) (Table 2). Most patients presented with a single neurological manifestation, while a smaller proportion presented with two or three concurrent manifestations (75.5%, 20.4%, and 4.1%, respectively).

Factors associated with the syndrome of irreversible lithium-effectuated neurotoxicity and predictive model performance

To identify factors associated with the diagnosis of SILENT and to support early post-discharge risk stratification, we examined candidate predictors in univariable analyses and then fitted a parsimonious multivariable logistic regression model (Table 3, Table S2). In the adjusted analysis, older age, acute-on-chronic lithium poisoning, ataxia, and higher overall clinical severity (PSS ≥2) were retained as key predictors of SILENT at 60 days. Myoclonic jerks and peak urea were also included in the final prediction model to capture neurological severity and renal biochemical involvement, despite more modest univariable associations (Table 3).

Table 2. Clinical characterization of SILENT at 60 days ($n=49$).

Neurological clinical manifestation	*n* (%)
Cerebellar dysfunction	12 (24.5)
Extrapyramidal symptoms	20 (40.8)
Brainstem dysfunction	4 (8.2)
Cognitive impairment/dementia	14 (28.6)
Vertical nystagmus	0 (0)
Retrobulbar optic neuritis	0 (0)
Persistent papilledema	0 (0)
Choreoathetotic movements	1 (2.0)
Peripheral neuropathy	3 (6.1)
Myopathy	3 (6.1)
Blindness	0 (0)
Other symptoms	6 (12.2)

Model discrimination was good on receiver operating characteristic analysis (Figure 2), with an AUC of 0.813 (SE 0.036; 95% CI 0.743–0.882; $P<0.001$).

Calibration by deciles showed overall acceptable agreement between observed and predicted risk, with close concordance in the highest-risk deciles (decile 10: predicted 0.40 vs observed 0.38; decile 9: predicted 0.17 vs observed 0.20) and greater variability in intermediate-risk strata, consistent with the low event

Table 3. Univariable and multivariable logistic regression analysis for SILENT at 60 days.

Variable	Category/unit	% SILENT (*n/N*)	Univariable or (95% CI)	*P*	Multivariable or (95% CI)	*P*
Age	Per one-year increase	–	1.05 (1.02–1.08)	<0.001	1.03 (1.003–1.07)	0.033
Poisoning type	Acute (ref)	5/136 (3.7)	–	–	–	–
	Acute-on-chronic vs acute	25/196 (12.8)	3.83 (1.43–10.27)	0.008	4.48 (1.17–17.23)	0.029
	Chronic vs acute	19/312 (6.1)	1.70 (0.62–4.65)	0.302	1.66 (0.44–6.24)	0.456
Peak urea	Per 1 mmol/L increase	–	1.01 (1.004–1.02)	0.003	1.006 (0.99–1.014)	0.163
Ataxia	No (ref)	31/524 (5.9)	–	–	–	–
	Yes	18/120 (15.0)	2.81 (1.51–5.21)	0.001	4.62 (2.13–10.03)	<0.001
Myoclonus	No (ref)	39/597 (6.5)	–	–	–	–
	Yes	10/47 (21.3)	3.87 (1.79–8.35)	0.001	2.37 (0.83–6.72)	0.106
PSS ≥2	No (ref)	12/349 (3.4)	–	–	–	–
	Yes	37/293 (12.6)	4.06 (2.07–7.94)	<0.001	2.35 (1.06–5.23)	0.036

Notes: OR, odds ratio; CI, confidence interval; PSS, Poisoning Severity Score. "ref" indicates the reference category. Continuous variables (Age, Peak urea) are modeled as linear terms; the OR represents the change per one-unit increase in the variable's reported unit (years for Age, mmol/L for Peak urea). The multivariable model includes all variables shown in this table. To convert urea from mmol/L to mg/dL, multiply by 2.801.

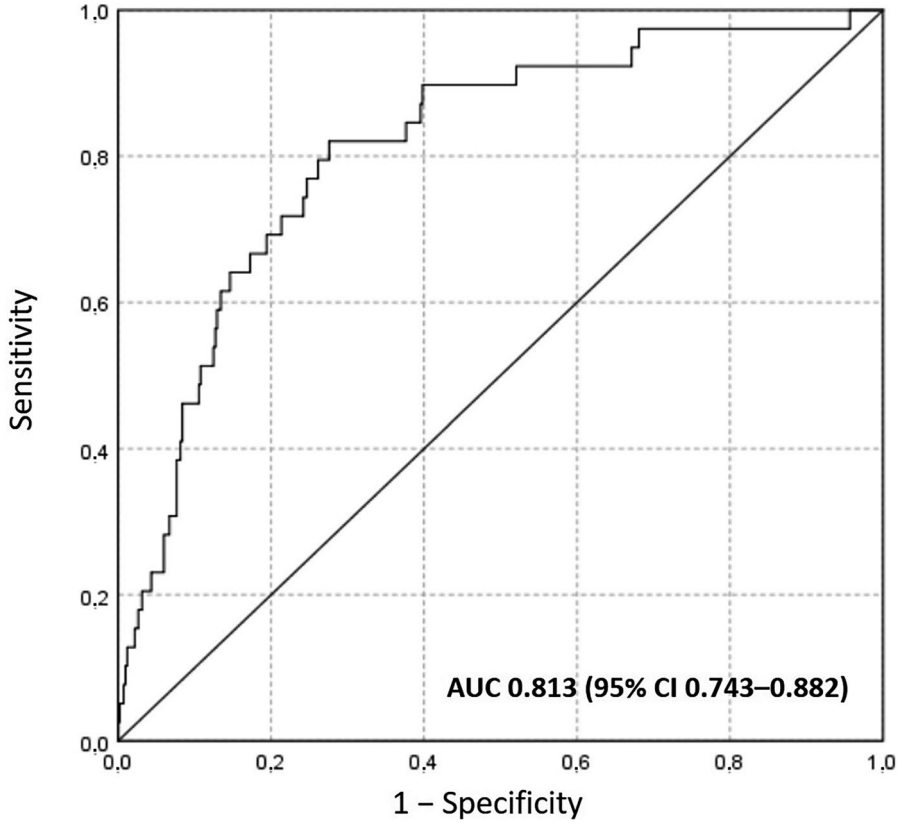

Figure 2. Receiver operating characteristic (ROC) curve of the multivariable prediction model for SILENT at 60 days.

rate and limited sample size per stratum (Table S5; complete-case analysis).

Because the intended clinical use was screening (minimizing missed cases), a low predicted-probability threshold ($P \geq 0.0475$) was selected (Figure 3). The 60-day outcome (SILENT yes/no) ascertainment was available for all included episodes (n = 644). Predicted probabilities, however, could only be computed in 456 episodes because 188 episodes had missing data in one or more model covariates; therefore, model performance was evaluated in complete cases. In complete cases (n = 456), the screening threshold classified 235/456 (51.5%) episodes as candidates for follow-up and identified 35 of 39 SILENT cases (sensitivity 89.7%). Specificity was 52.0%, with a positive predictive value of 14.9% and a negative predictive value of 98.2% (Table 4).

For clinical implementation, an additional, more specific high-risk threshold was explored to define a smaller subgroup for intensified follow-up. Using a high-risk threshold of ≥0.18, 59/456 (12.9%) episodes were classified as high risk, with specificity 90.2% and positive predictive value 30.5%, at the cost of lower sensitivity (46.2%); comparative performance across screening and high-risk thresholds is shown in Supplementary Table S3.

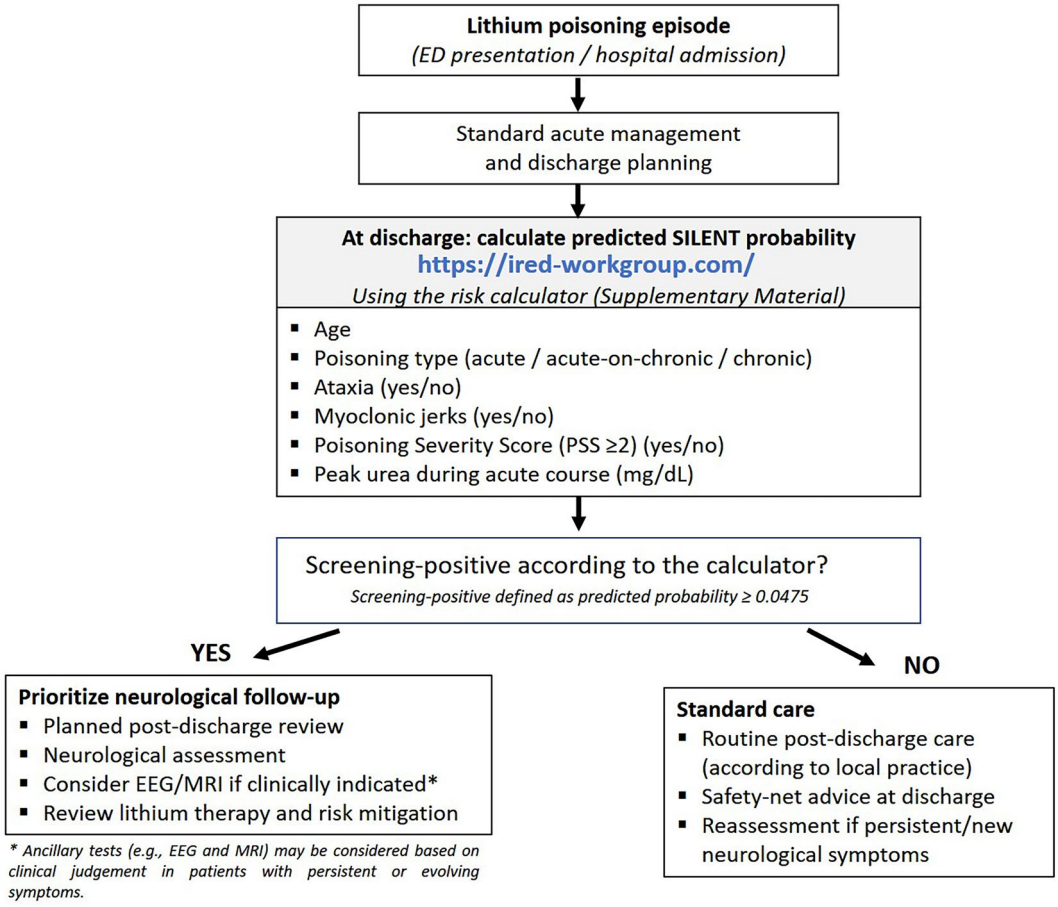

Figure 3. Model-based screening approach to guide post-discharge neurological follow-up after lithium poisoning. The predicted probability is computed using the SILENT-60 Risk Calculator (Supplementary File S1). https://ired-workgroup.com/.

Table 4. Model-based classification using the screening threshold ($n = 456$).

Model-based classification	SILENT ($n = 39$)	Non-SILENT ($n = 417$)	Total ($n = 456$)
Candidate for follow-up (≥0.0475)	35 (89.7%)	200 (48.0%)	235 (51.5%)
Not a candidate for follow-up (<0.0475)	4 (10.3%)	217 (52.0%)	221 (48.5%)
Total	39 (100%)	417 (100%)	456 (100%)

Notes: Values are presented as *n* (%). Classification was based on the predicted probability of SILENT at 60 days, using the screening threshold (predicted probability ≥0.0475).

In internal split-sample validation (random 70/30 split), discrimination in the 30% validation subset remained acceptable (AUC 0.730 [SE 0.080], 95% CI 0.572–0.888; $P = 0.009$), evaluated in complete cases with predictor data ($n = 121$). Applying the screening threshold classified 60/121 (49.6%) episodes as candidates for follow-up and identified 10 of 12 SILENT cases (sensitivity 83.3%), with specificity 54.1%, positive predictive value 16.7% and negative predictive value 96.7% (TP = 10, FN = 2, TN = 59, FP = 50). Discrimination was lower in the validation subset but remained acceptable.

Discussion

In this large, international, multicenter cohort of lithium poisoning episodes, SILENT was identified in 7.6% of cases, a proportion notably higher than suggested by the existing literature [14], which is largely based on isolated case reports and small series. Patients who developed SILENT were older and more frequently presented with acute-on-chronic poisoning, greater clinical severity, and early neurological manifestations, while serum lithium concentrations were not associated with the development of persistent neurotoxicity. The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity occurred both in episodes treated with RRT and in episodes without RRT, including some that retrospectively met EXTRIP-recommended or EXTRIP-suggested criteria. However, given the observational design, these findings should not be interpreted as establishing

whether individual cases were preventable with RRT. Nevertheless, the finding that 22 of 37 (59.5%) SILENT episodes without RRT retrospectively fulfilled at least EXTRIP-suggested criteria highlights a potential gap in treatment adherence. Although the retrospective design precludes any inference regarding preventability in these specific cases, this observation suggests that systematic application of EXTRIP-based RRT indications in eligible lithium-poisoned patients may warrant prospective evaluation in the context of SILENT prevention, and represents a tangible area for clinical improvement. Building on these findings, we developed and internally validated a pragmatic prediction model based on routinely available clinical variables, which demonstrated good discrimination (AUC 0.813) and a high negative predictive value, supporting its potential utility for early post-discharge risk stratification.

Our findings suggest that the risk of the SILENT at 60 days follows a recognizable clinical pattern at the index poisoning episode rather than occurring at random. Predictors clustered around the exposure pattern—particularly acute-on-chronic poisoning—neurological involvement, and overall poisoning severity during the acute presentation. These results support the concept that bedside features readily available in emergency care can identify a subgroup of patients in whom delayed or persistent neurotoxicity is more likely and for whom structured post-discharge surveillance is reasonable.

Neurological manifestations during the index episode, especially ataxia and myoclonus, emerged as clinically meaningful markers of central nervous system involvement. These features are straightforward to assess across diverse clinical settings and may reflect early or established neuronal injury. Similarly, a higher PSS captures global illness burden and integrates clinical features not fully represented by isolated laboratory values, reinforcing the relevance of the overall acute phenotype for risk stratification beyond lithium concentrations alone [19].

Renal biochemical abnormalities during the acute episode likely reflect impaired lithium clearance and overall episode severity [19–21]. Although renal markers such as urea and creatinine were associated with SILENT in univariable analyses, their independent contribution attenuated after multivariable adjustment, consistent with interrelation among renal measures and overlap with other indicators of clinical severity. These findings suggest that renal biochemistry alone is insufficient to guide follow-up decisions and is best interpreted as a complementary indicator within a multivariable clinical framework.

From a clinical perspective, targeted follow-up should prioritize patients with higher-risk index presentations, particularly those with acute-on-chronic exposure, overt neurological manifestations (eg, ataxia or myoclonus), higher overall poisoning severity, and biochemical evidence of impaired lithium clearance. Given the intended use of the model as a screening tool, a low predicted-probability threshold is appropriate to minimize missed cases, accepting reduced specificity. In practice, patients above this threshold may benefit from planned neurological follow-up, whereas those below the threshold can generally be managed with standard care and explicit safety-net advice. The proposed follow-up approach translates this strategy into a pragmatic framework for follow-up prioritization. It is not intended to guide emergency-department disposition (admission vs discharge) or to influence indications for extracorporeal treatment, which should remain based on clinical assessment and current recommendations. Ancillary investigations were not systematically captured in this retrospective dataset and therefore were not analyzed as part of the 60-day outcome assessment. In higher-risk patients or when symptoms persist or evolve, EEG may be useful to support clinical assessment and monitoring of lithium neurotoxicity, as suggested by prior reports and experimental data [22–24]. Neuroimaging (eg, MRI) may also be considered based on clinical judgment, particularly when the clinical course is atypical or progressive.

Model calibration by deciles showed overall acceptable agreement between observed and predicted risk, with close concordance in the highest-risk strata and greater variability in intermediate-risk strata, consistent with the low event rate and the limited sample size within each decile (Table S5; complete-case analysis).

Associations between specific acute management strategies or disposition and SILENT should be interpreted cautiously, as they are strongly influenced by baseline severity, local protocols, and resource availability [25,26]. As such, these relationships are more consistent with confounding by indication than with causal effects. Importantly, the present approach focuses on predictors available at the index presentation to guide follow-up prioritization rather than attributing outcomes to individual interventions. This is particularly relevant when interpreting the relationship between EXTRIP-based RRT indications and later SILENT, as retrospective adherence analyses in an observational cohort cannot determine preventability.

This study has several strengths, including its large, multicenter international design, which enhances generalizability across healthcare settings, and the use of routinely available clinical variables that support real-world

applicability. The 60-day outcome horizon is clinically meaningful, capturing delayed or persistent neurological sequelae relevant to post-discharge decision-making. Limitations inherent to retrospective observational studies remain. Outcome ascertainment and follow-up intensity may have varied across centers, introducing potential misclassification and detection bias. Predicted probabilities could be computed in 456/644 episodes; therefore, model performance and calibration were evaluated in complete cases, which may introduce selection bias if missingness is not random, and residual confounding cannot be excluded. Internal validation used a split-sample approach, and external validation and prospective evaluation are therefore needed.

Future work should prioritize external validation and prospective implementation to evaluate calibration, clinical utility, and resource impact of risk-guided follow-up after lithium poisoning. If validated, integrating the risk estimate and follow-up pathway into discharge routines could help standardize post-discharge surveillance while preserving clinical judgment.

Conclusion

Syndrome of Irreversible Lithium-Effectuated Neurotoxicity is a clinically relevant complication of lithium poisoning that cannot be predicted by serum lithium concentrations alone and often follows a recognizable clinical pattern at presentation. Patients with acute-on-chronic exposure, neurological manifestations, and greater overall severity are at higher risk of persistent neurotoxicity. A simple model based on routinely available clinical variables may help identify patients who warrant structured neurological follow-up after discharge, supporting earlier recognition of delayed sequelae and more targeted use of clinical resources.

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Ethical approval

All authors confirm the maintenance of confidentiality and respect for patients' rights in the author responsibilities document, the publication agreement, and the transfer of rights to the journal. For the Spanish cohort, the study was approved by the Comité de Ética de la Investigación con Medicamentos (CEIm) of Hospital Universitario Puerta de Hierro Majadahonda (EOM 22/23); for the Irish cohort, by the SJH/TUH Research Ethics Committee (Project ID 3733); and for the Swiss cohort, by the Ethikkommission Nordwest und Zentralschweiz (Project ID 2024-00321).

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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