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A TDM-Driven Closed-Loop Pharmaceutical Care Model for Toxicity Management in Pediatric Patients Receiving High-Dose Methotrexate: Impact on Supportive Care Outcomes

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Abstract

Objectives To evaluate the impact of a closed-loop pharmaceutical care model, integrated with a therapeutic drug monitoring (TDM) tracking system, on reducing chemotherapy-related toxicity and enhancing the quality of supportive care in pediatric patients with acute lymphoblastic leukaemia (ALL) receiving high-dose methotrexate (HD-MTX).

Methods A pre–post interventional study was conducted at the Pediatric Hematology Department of Fujian Medical University Union Hospital. The intervention involved integrating a TDM intelligent tracking system into the hospital information system, which provided automated identification of high-risk patients, real-time concentration monitoring, abnormal result alerts, and pharmacist-led dose adjustments and rescue protocols. Clinical data from 189 HD-MTX cycles in the pre-intervention period (January 2019 to June 2020) were compared with those from 160 cycles in the post-intervention period (June 2024 to December 2025). Outcome measures included the incidence of severe hypermethotrexatemia,, the occurrence of grade III–IV oral mucositis, medication order rejection rates, and antimicrobial use density (AUD).

Results Post-intervention, severe hypermethotrexatemia decreased from 3.70% to 0.63% (Fisher's exact test, $P = 0.068$); grade III–IV oral mucositis declined from 8.47% to 3.13% ($P = 0.047$); medication order rejection rates fell from 10.32% to 7.69% ($\chi^2 = 121.3$, $P < 0.001$); and antibiotic use density dropped from 80.22 to 69.66.

Conclusion The TDM-driven closed-loop pharmaceutical care model significantly reduced severe HD-MTX-related toxicities, improved medication rationality, and optimized antibiotic stewardship, providing a replicable framework for pharmacist-led toxicity management in pediatric oncology supportive care.

Clinical trial number: not applicable.

Keywords Therapeutic drug monitoring; High-dose methotrexate; Pediatric acute lymphoblastic leukemia; Supportive care; Toxicity management; Clinical pharmacist

1.Introduction

Pediatric acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for approximately 72.6% of all childhood leukemias in China, with an estimated incidence of 34.3 per million children aged 0–14 years in 2020 [1]. Although 5-year survival rates now exceed 90% in high-income countries [2], the treatment journey remains protracted and complex, typically spanning 1.5 to 3 years of multi-agent, multi-course chemotherapy. Among the agents used, high-dose methotrexate (HD-MTX) is a cornerstone of consolidation therapy across nearly all contemporary ALL protocols.

However, HD-MTX presents substantial supportive care challenges. Its narrow therapeutic window, combined with considerable interindividual pharmacokinetic variability—particularly in children whose immature organ systems and enzymatic pathways render them especially susceptible to unpredictable drug disposition—places patients at significant risk for severe toxicities, including nephrotoxicity, grade III–IV oral mucositis, and myelosuppression [3]. These adverse effects not only impair patients' quality of life and prolong hospitalization but also substantially increase healthcare resource utilization [3]. Even with overall survival exceeding 90%, safe and effective delivery of HD-MTX remains a major clinical challenge, underscoring the critical need for precision in dosing and toxicity management.

Therapeutic drug monitoring (TDM) is essential for HD-MTX administration, as delayed elimination correlates closely with the risk and severity of toxicity [4]. Effective TDM, however, requires more than laboratory measurements; it demands a systematic, closed-loop system that ensures timely sampling, accurate result interpretation, prompt clinical decision-making, and consistent follow-up. In many real-world settings, gaps in this loop—missed monitoring, delayed rescue, or incomplete documentation—continue to compromise patient safety and the quality of supportive care.

Against this backdrop, a national policy initiative has created new opportunities for pharmacist engagement. In January 2024, the National Health Commission of China launched a pilot program for ward-based clinical pharmacist services across 94 hospitals nationwide [5], mandating the integration of pharmacists into inpatient care teams. This policy provides an institutional framework for pharmacists to assume active roles in TDM-guided toxicity management. Yet, despite this impetus, few studies have systematically evaluated the impact of pharmacist-led, technology-enabled closed-loop TDM models on supportive care outcomes in pediatric oncology.

To address this gap, we developed and implemented a TDM intelligent tracking system integrated with the hospital information system (HIS) in our pediatric hematology unit. This system enables ward-based pharmacists to proactively manage the entire HD-MTX monitoring-to-rescue cycle, from high-risk patient identification and real-time concentration tracking to alert-triggered interventions and documentation. This study evaluates the effectiveness of this model in reducing HD-MTX-related toxicities and improving quality indicators of supportive care, with the goal of providing a replicable framework for pharmacist-led TDM services in pediatric oncology settings.

2. Methods

2.1 Study Design and Setting

This was a non-randomized pre–post interventional study with historical control conducted in the Pediatric Hematology Department of Fujian Medical University Union Hospital, a tertiary teaching hospital in Fujian, China. The intervention—a TDM-driven closed-loop pharmaceutical care model—was implemented in March 2024. Pre-intervention data were collected from January 2019 to June 2020 (routine pharmaceutical care without the TDM tracking system)[6], and post-intervention data from June 2024 to December 2025 (after full system implementation and workflow stabilization).

2.2 Study Population

Inclusion criteria were: (1) age ≤14 years; (2) newly diagnosed ALL according to bone marrow morphology, immunophenotyping, cytogenetics, and molecular biology; (3)newly diagnosed, treatment-naïve ALL; and(4)receipt of HD-MTX chemotherapy at our center. Exclusion criteria were: (1) severe hepatic or renal insufficiency at baseline; and (2) history of MTX hypersensitivity.

A total of 349 HD-MTX cycles were included: 189 cycles in the pre-intervention group (189 patients) and 160 cycles in the post-intervention group (160 patients). Baseline characteristics are presented in Table 1. Sex, immunophenotype, and ETV6-RUNX1 and BCR-ABL1 fusion gene distributions were comparable between groups ($P > 0.05$). Age distribution differed significantly ($P < 0.001$) and was adjusted for as a covariate.

Table 1 Baseline characteristics of patients in the Pre- and Post-intervention groups

Characteristic	Pre-intervention (n = 189)[6]	Post-intervention (n = 160)	*P* value
Sex, n (%)			0.291
Male	118(62.4)	91(56.9)	
Female	71(37.6)	69(43.1)	
Age, years, n (%)			< 0.001
≥10	20(10.6)	45(28.1)	
1-10	167(88.4)	111(69.4)	
＜1	2(1.0)	4(2.5)	
Immunophenotype, n (%)			0.271
B-cell	165(87.3)	133(83.1)	
T-cell	24(12.7)	27(16.9)	
ETV6-RUNX1 fusion, n (%)			0.173

Positive	39(20.6)	24(15.0)	
Negative	150(79.4)	136(85.0)	
BCR-ABL1 fusion, n (%)			0.863
Positive	9(4.8)	7(4.4)	
Negative	180(95.2)	153(95.6)	

Notes: Data are presented as number (%) unless otherwise indicated. P values were calculated using the chi-square test or Fisher's exact test, as appropriate. The age distribution differed significantly between groups and was adjusted for as a covariate in subsequent analyses.

2.3 Intervention: The TDM-Driven Closed-Loop Pharmaceutical Care Model

The intervention consisted of a TDM intelligent tracking system integrated into the HIS, enabling ward-based pharmacists to manage a complete closed loop from risk identification to post-monitoring follow-up.

2.3.1 System Core Functions

(1) Automated high-risk patient identification: The system flagged patients prescribed high-risk drugs (e.g., MTX, vancomycin) under the "TDM-recommended population" module. When an HD-MTX order was entered, "Methotrexate" appeared in the system, immediately alerting the pharmacist to initiate monitoring.

(2) Real-time TDM execution tracking: A status field ("TDM performed: Yes/No") displayed whether the monitoring order had been placed. Pharmacists actively monitored this field and reminded physicians to place orders when blank, preventing missed sampling.

(3) Abnormal result alerts: When TDM results exceeded reference ranges, the system sent real-time alerts to both the pharmacist and the attending physician. For example, when the 44-hour MTX concentration exceeded 10 μmol/L—indicating severe delayed elimination—the system immediately displayed a pop-up alert to the ward-based clinical pharmacist and the attending physician, triggering the emergency response protocol, which included transfer to the intensive care unit for continuous renal replacement therapy.

2.3.2 Pharmacist-Led Clinical Workflow

Pre-chemotherapy assessment: Before the first HD-MTX cycle, the pharmacist assessed the child's endogenous creatinine clearance to evaluate renal function. For subsequent cycles, the pharmacist reviewed prior MTX concentration results and post-discharge adverse events, as subsequent MTX doses were adjusted based on prior clearance patterns. After the physician placed the HD-MTX order and the system flagged the patient, the pharmacist set individualized monitoring time points based on body surface area, baseline liver/kidney function, and prior MTX clearance history. Routine monitoring included 20-hour and 44-hour concentrations. For high-risk patients (prior 44-hour MTX >1 μmol/L, severe mucositis history, or renal impairment), an additional 16-hour point was added. For patients with 44-hour MTX >1 μmol/L, further 68-hour or 72-hour monitoring was added until concentrations fell below 0.1 μmol/L.

TDM and rescue: The pharmacist monitored the "TDM performed" status field and reminded

physicians when orders were missing. Upon obtaining concentration results, the pharmacist interpreted them according to the Chinese Children's Cancer Group ALL-2025 protocol [7] and provided recommendations to the attending physician, including: (1) risk stratification (safe/alert/danger zones); (2) calcium folinate dose adjustment (e.g., escalating from 15 mg/m² every 6 hours × 3 doses to 30 mg/m², as detailed in Table 2,Part A); and (3) enhanced supportive measures (increased hydration rate, urine alkalinization, diuretic use) [7].All pharmacist recommendations are reviewed and confirmed by the physician before execution, with all interventions documented in the pharmaceutical care record. The complete pharmacist-led workflow is summarized in Figure 1.

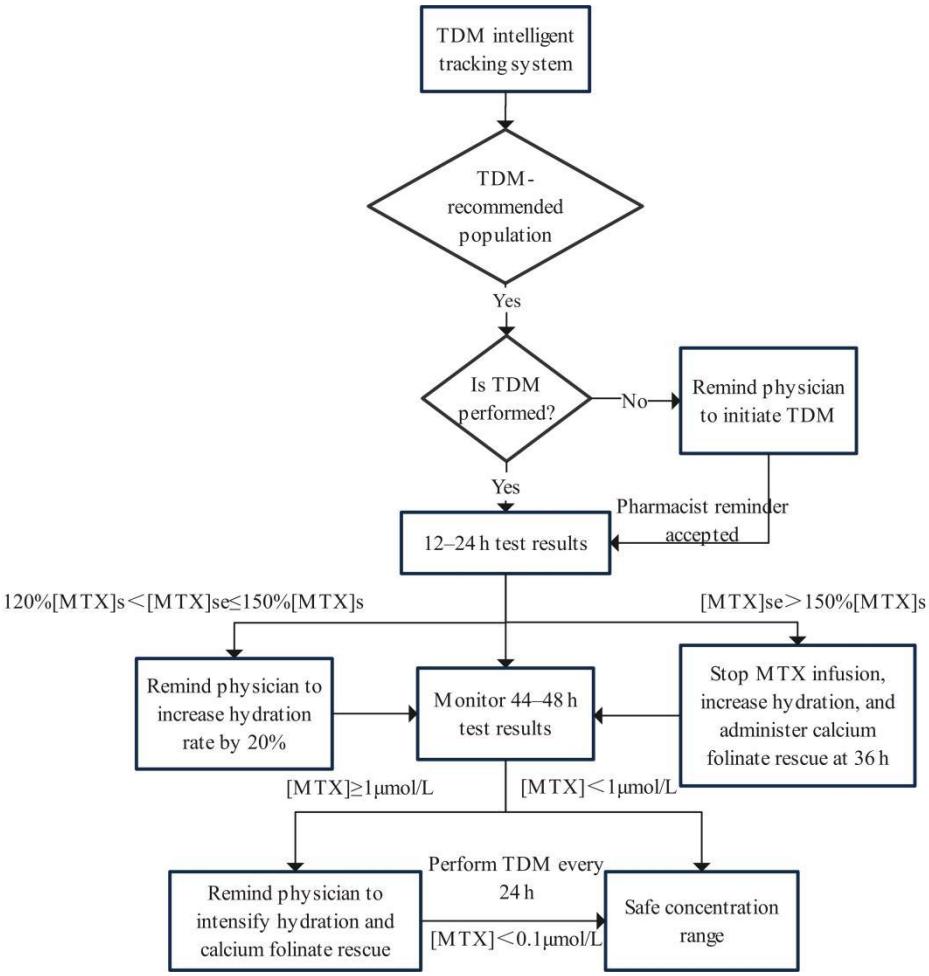


Fig. 1 TDM-based MTX concentration monitoring and rescue protocol flowchart.

Adverse event prevention and management: The pharmacist conducted daily ward rounds and provided verbal and written education to parents on early recognition of mucositis, rash, and hepatotoxicity. Specific measures included:

- Nephrotoxicity prevention: Close monitoring of serum creatinine, BUN, electrolytes, pH, and urine output for early acute kidney injury detection.
- Mucositis prevention and management: Individualized mouthwash regimens (Table 2,PartB); dietary guidance (avoiding hot, hard, spicy, acidic, or rough foods; ensuring adequate protein, B vitamins, vitamin C, and zinc); instruction on proper rinsing technique (1–3 minutes, 3–4 times daily, after meals and before bed, with increased frequency during high-risk periods; no food or water for 30 minutes after rinsing); daily oral cavity examination with WHO grading (grade 1–4); for discharged patients, follow-up via the online community (described in a separate report).

- Myelosuppression monitoring: Blood counts monitored twice weekly via the online community; 6-mercaptopurine withheld when ANC <0.5×10⁹/L, WBC <1.5×10⁹/L, or PLT <50×10⁹/L [7].
- Other toxicities: Hepatotoxicity, neurotoxicity, and skin rash were also monitored.

Table 2 Supportive care and rescue protocols

Part A: Calcium folinate dosing and hydration rate adjustment based on MTX concentrations

MTX Concentration at 44–48 h (μmol/L)	MTX Concentration at 68–72 h (μmol/L)	Calcium Folinate (per dose, mg/m²)	Hydration Rate (mL/m²/h)
≤1.0	≤0.4	15	150
1.0＜[MTX]≤2.0	0.4＜[MTX]≤0.5	30	150
2.0＜[MTX]≤3.0	0.5＜[MTX]≤0.6	45	175
3.0＜[MTX]≤4.0	0.6＜[MTX]≤0.8	60	175
4.0＜[MTX]≤5.0	0.8＜[MTX]≤1.0	75	200
5.0＜[MTX]≤6.0	1.0＜[MTX]≤1.5	90	200
6.0＜[MTX]≤7.0	1.5＜[MTX]≤2.0	100	200
7.0＜[MTX]≤8.0	2.0＜[MTX]≤3.0	120	200
8.0＜[MTX]≤9.0	3.0＜[MTX]≤4.0	140	200
9.0＜[MTX]≤10	4.0＜[MTX]≤5.0	160	200
＞10	＞5.0	200+CRRT+PE	

Abbreviations: MTX, methotrexate; CRRT, continuous renal replacement therapy; PE, plasma exchange.

Part B: Individualized mouthwash regimens for oral mucositis prevention and management

Patient Type	Mouthwash Regimen	Timing of Use
ALL patients undergoing routine inpatient chemotherapy	Normal saline or cetylpyridinium chloride mouthwash	Use daily in the morning, at bedtime, and after each meal during chemotherapy.
ALL patients with a history of oral mucosal damage following prior HD-MTX chemotherapy	Calcium folinate (CF) ice-cold solution: 15 mg CF in 100 mL normal saline [8]	Administer on days 3–7 after chemotherapy, during the peak period of mucositis risk.
ALL patients with concurrent oral thrush (candidiasis) during chemotherapy	Sodium bicarbonate solution (2.5%) [9]	Initiate promptly upon symptom onset.
ALL patients developing oral ulcers during chemotherapy	Kangfuxin Liquid [10]	Initiate promptly upon symptom onset.

Notes for Table 2:

For Part A: MTX concentrations should be rechecked every 24 h until the level falls below 0.1 μmol/L, at which point rescue therapy is discontinued. If the hydration rate is ≥175 mL/m²/h, addition of a diuretic (acetazolamide preferred; furosemide not recommended) is advised.

For Part B: All mouthwash regimens are monitored by the ward-based clinical pharmacist. The CF ice-cold solution should be prepared fresh and used within 24 h.

All dose adjustments and protocol decisions adhere to the Chinese Children's Cancer Group ALL-2025 protocol [7].

2.4 Outcome Measures

Primary outcomes:
Incidence of severe hypermethotrexatemia (MTX concentration >10 μmol/L with clinical toxicity);
Incidence of grade III–IV oral mucositis (WHO grading).
Secondary outcomes:
Medication order rejection rate (number of rejected orders / total orders reviewed, reflecting prescribing rationality);
Antimicrobial use density (AUD): calculated as follows:
AUD = (Σ DDDs of all antimicrobials / Total patient-days) × 100
Total patient-days was estimated as the number of discharged patients × average length of stay.
Inpatient drug cost ratio (drug costs / total inpatient costs).

Of note, the primary toxicity outcomes (Table 3) were calculated per HD-MTX cycle, with pre- and post-intervention periods defined as January 2019–June 2020 and June 2024–December 2025, respectively. In contrast, the medication order rejection rate, antimicrobial use density, and drug cost ratio (Tables 4 and 5) were derived from annual hospital administrative data for the full calendar years 2024 and 2025, as these metrics are routinely reported on a yearly basis. The intervention was initiated in March 2024; therefore, 2024 represents the early post-implementation phase and 2025 the stabilized phase.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the t-test or Mann–Whitney U test. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1 Severe Hypermethotrexatemia

The incidence of severe hypermethotrexatemia decreased from 3.70% (7/189) in the pre-intervention group to 0.63% (1/160) in the post-intervention group (Fisher's exact test, $P = 0.068$) (Table 3). Although the difference did not reach statistical significance, the absolute risk reduction of 3.07 percentage points is clinically meaningful.

3.2 Grade III–IV Oral Mucositis

Grade III–IV oral mucositis occurred in 16 of 189 cycles (8.47%) pre-intervention and 5 of 160 cycles (3.13%) post-intervention. This reduction was statistically significant (Fisher's exact test, $P = 0.047$)

(Table 3).

Table 3 Primary Toxicity Outcomes

Outcome	Pre-intervention (Jan 2019 – Jun 2020; n=189 cycles) [6]	Post-intervention (Jun 2024 – Dec 2025; n=160 cycles)	*P* value*
Severe hypermethotrexatemia, n (%)	7(3.70)	1(0.63)	0.068
Grade III–IV oral mucositis, n (%)	16 (8.47)	5 (3.13)	0.047

Note: Data were analyzed using Fisher's exact test. A two-sided *P* value < 0.05 was considered statistically significant.

Footnotes for Table 3:The pre-intervention period (Jan 2019 – Jun 2020) represents routine pharmaceutical care without the TDM tracking system. The post-intervention period (Jun 2024 – Dec 2025) represents care after full system implementation and workflow stabilization.

3.3 Medication Order Rejection Rate

The medication order rejection rate decreased significantly from 10.32% (2,056/19,919 orders) in 2024 to 7.69% (3,291/42,799 orders) in 2025 (χ^2 = 121.3, P < 0.001) (Table 4). Monthly trend analysis (Figure 1) showed that rejection rates, which exceeded 15% in January–February 2024, dropped sharply to 8.91% after the pharmacist's formal integration in March 2024, and continued to decline through 2025, with all monthly rates below 8% in the second half of the year.

3.4 Antimicrobial use density (AUD)

Antimicrobial use density (AUD) decreased from 80.22 in 2024 to 69.66 in 2025, representing a 13.2% relative reduction (Table 4).

Table 4 Prescribing Rationality and Antimicrobial Use

Indicator	2024 (Early post-implementation)	2025 (Stabilized post-implementation)	*P* value*/Change
Medication order rejection rate, n/N (%)	2,056 / 19,919 (10.32)	3,291 / 42,799 (7.69)	<0.001
Antimicrobial use density	80.22	69.66	–13.2%

Data for these indicators were extracted from annual hospital statistics for the full calendar years 2024 and 2025. The intervention was fully implemented in March 2024; thus, 2024 represents the early post-implementation phase, and 2025 represents the stabilized post-implementation phase.

*P value calculated using the chi-square test (χ^2 = 121.3). The change in antimicrobial use density is expressed as a relative reduction.

3.5 Inpatient Drug Cost Ratio

The inpatient drug cost ratio decreased from 46.72% in 2024 to 45.54% in 2025 (paired t = 0.738, P = 0.476) , showing a downward trend that did not reach statistical significance.

4. Discussion

This study demonstrates that a pharmacist-led, TDM-driven closed-loop pharmaceutical care model significantly reduces severe HD-MTX-related toxicities—particularly grade III–IV oral mucositis—and

improves medication rationality in pediatric ALL patients. These findings have important implications for supportive care practice.

4.1 Contribution to Supportive Care

The most clinically significant finding is the reduction in severe oral mucositis from 8.47% to 3.13% (P = 0.047). Oral mucositis is one of the most debilitating toxicities of HD-MTX, causing severe pain, nutritional compromise, increased infection risk, and prolonged hospitalization [11]. Our intervention achieved this improvement through a combination of TDM-guided precise calcium folinate rescue—preventing both under-rescue (which allows toxicity) and over-rescue (which may antagonize efficacy)—and a structured mucositis prevention package including individualized mouthwash regimens, dietary counseling, and daily monitoring.

The reduction in severe hypermethotrexatemia from 3.70% to 0.63%, while not statistically significant, represents a clinically meaningful improvement. The lack of statistical significance may reflect the relatively low baseline incidence and limited sample size; a larger multicenter study would be needed to confirm this trend.

4.2 Mechanism of Action: The Closed-Loop Advantage

The key innovation of our model is the in-hospital closed-loop design. Previous studies have reported isolated TDM services or pharmacist consultations, but gaps between monitoring and action often compromise effectiveness [12,13]. Our system closes the loop through four integrated features: (1) automated identification ensures no high-risk patient is overlooked; (2) real-time tracking prevents missed sampling; (3) immediate alerts enable rapid intervention; and (4) pharmacist documentation and follow-up complete the cycle within the hospital setting. This design is consistent with MASCC's emphasis on "comprehensive, multidisciplinary, and continuous" supportive care [14,15].

It should be noted that the present study focuses exclusively on the in-hospital TDM-driven closed loop. The post-discharge continuity of care—including an online pharmacist-led patient community that provides real-time medication guidance and adverse event monitoring—represents a complementary, parallel component of our overall care model. This off-campus virtual care component operates independently for all pediatric hematology patients at our institution, regardless of treatment phase, and is the subject of a separate report.

4.3 Impact on Healthcare Quality

The significant reduction in medication order rejection rates—from >15% to <8%—reflects the pharmacist's embedded role in the clinical team. By reviewing orders prospectively, the pharmacist prevented potential prescribing errors before they reached patients, addressing a critical patient safety concern in pediatric oncology where dosing errors can have severe consequences. The concurrent reduction in antibiotic use density suggests improved infection complication management, possibly through better mucositis prevention and more judicious antimicrobial prescribing.

4.4 Limitations

Several limitations should be acknowledged. First, the single-center, pre–post design may introduce temporal confounding, and unmeasured changes in practice over the study period could have contributed to the observed improvements. Second, the age distribution differed significantly between

groups, though this was adjusted for in the analysis. Third, the study focused on a single chemotherapy agent (MTX) at a single institution; generalizability to other drugs and settings requires further investigation. Fourth, the lack of statistical significance for hypermethotrexatemia reduction may reflect insufficient power; larger studies are warranted.

4.5 Future Directions

Future work should include: (1) multicenter studies with larger sample sizes to confirm these findings; (2) randomized controlled or stepped-wedge designs to strengthen causal inference; and (3) expansion of the TDM-driven model to other high-risk chemotherapeutic agents (e.g., vincristine, methotrexate in other protocols). Beyond these research priorities, we are actively operating a separate, well-established online pharmaceutical care service—a pharmacist-led virtual patient community that provides real-time medication counseling and adverse event surveillance for all pediatric hematology patients after hospital discharge. This virtual care loop, which ensures continuous oversight beyond the hospital stay, has been implemented as an ongoing clinical service and is described in detail in our companion article.

5. Conclusion

The TDM-driven closed-loop pharmaceutical care model, led by ward-based clinical pharmacists, significantly reduced severe HD-MTX-related oral mucositis and improved medication rationality in pediatric ALL patients. This model offers a practical, replicable framework for pharmacist-led toxicity management that aligns with the principles of comprehensive supportive care.

Declarations

Ethics approval This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Fujian Medical University Union Hospital on February 13, 2018 (Approval No. [2018] Xie Yuan No. 52).

Informed consent Informed consent was obtained from all subjects involved in the study. We confrm all patient/personal identifers have been removed or disguised so the patient/person(s) described are not identifable and cannot be identifed through the details of the story.

Competing Interests The authors declare no competing interests.

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Author contributions Xuemei Wu, Bin Zheng, and Maobai Liu conceptualized and designed the overall study framework, with a specific focus on the TDM-driven closed-loop pharmaceutical care model for HD-MTX toxicity management. Binglin Huang designed, developed, and implemented the TDM intelligent tracking system integrated into the hospital information system, and was responsible for its ongoing maintenance and operational coordination. Yu Cheng performed all plasma methotrexate concentration measurements and issued the corresponding laboratory reports. Shaohua Le were responsible for patient recruitment and screening according to the predefined inclusion and exclusion criteria, as well as the execution of physician orders within the TDM closed-loop system. Weiwei Zheng, as the ward-based clinical pharmacist in the pediatric hematology department, delivered the full-spectrum pharmaceutical care throughout the TDM workflow, including pre-chemotherapy assessment, individualized TDM monitoring, calcium folinate dose adjustment recommendations, daily ward rounds, patient and caregiver education on oral mucositis prevention and early recognition, adverse event monitoring, and post-discharge home medication management. Weiwei Zheng and Binglin Huang were responsible for data collection; Weiwei Zheng and Binglin Huang performed data analysis and interpretation. The first draft of the manuscript was written by Weiwei Zheng. All authors critically reviewed and revised previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and analyzed during the current study are not publicly available due to patient privacy protection. Data are available from the corresponding author on reasonable request.

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