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A Multicenter Quality Improvement Program for Standardized Management of Chemotherapy-Induced Neutropenia in China: A Longitudinal Retrospective Evaluation

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Research Article

Keywords: chemotherapy-induced neutropenia, febrile neutropenia, supportive care, quality improvement, granulocyte colony-stimulating factor, risk assessment

Posted Date: November 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11616268/v1

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Additional Declarations: No competing interests reported.

Abstract

Chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) remain common complications of cytotoxic chemotherapy and require timely risk assessment and prevention. We conducted a retrospective evaluation of a multicenter quality-improvement program designed to standardize CIN/FN management across 61 participating centers in 54 hospitals in China. Monthly aggregate data were aligned to each center's implementation month; the pre-implementation month − 1 served as the baseline, for comparison against month 12 post-implementation. Following program rollout, CIN/FN risk assessment rates increased from 62.9% to 98.0%, overall primary prophylaxis coverage from 25.4% to 42.2%, primary prophylaxis in high-risk patients from 49.8% to 64.2%, and total prophylaxis in high-risk patients from 86.5% to 94.5% (all nominal $p < 0.0001$). Over the same period, FN incidence decreased from 11.5% to 3.0%, CIN incidence from 33.6% to 21.8%, and rates of antimicrobial treatment initiated after CIN/FN onset from 15.3% to 5.6% (all nominal $P < 0.0001$). Follow-up completion rates improved from 67.0% to 95.8%, myelosuppression-related readmission rates declined from 8.6% to 2.7%, and mean length of hospital stay was reduced by 1.04 days. Over the course of the intervention, an increasing number of centers adopted standardized and proactive management practices. Exploratory generalized estimating equation (GEE) suggested that distinct implementation features were associated with different parts of the care pathway—for example, risk assessment, prevention, follow-up, and readmission—rather than all influencing the same outcome. Overall, implementation of the program was associated with more widespread use of CIN/FN risk assessment and preventive measures, a lower observed burden of neutropenia-related events, and more complete follow-up. These findings should be interpreted in the constraints of the retrospective, nonrandomized study design, and as such do not establish a causal relationship between the program and the observed outcomes.

1 Introduction

Chemotherapy-induced neutropenia (CIN) is among the most frequent hematologic toxicities of cytotoxic anticancer treatment and remains an important dose-limiting adverse event. Severe neutropenia may progress to febrile neutropenia (FN), serious infection, emergency medical care, hospitalization, dose reduction, or treatment delay. These consequences extend beyond the acute neutropenic episode because interruption of planned anticancer therapy may compromise treatment delivery, while infection-related care and unplanned hospitalization add substantial burden to patients and healthcare systems [1–3].

Contemporary Chinese and international guidelines therefore place prospective CIN/FN risk assessment at the beginning of preventive decision-making. The 2026 China Anti-Cancer Association (CACA) guideline recommends assessment of the overall risk of first-cycle neutropenic fever, incorporating both regimen-related and patient-related factors, with primary prophylaxis for high-risk individuals and reassessment before subsequent cycles [1]. The 2023 Chinese consensus similarly emphasizes risk assessment, early recognition of FN and infection, and appropriate preventive and therapeutic measures [2]. The updated 2026 American Society of Clinical Oncology (ASCO) guideline continues to support

prophylactic use of hematopoietic colony-stimulating factors in patients whose overall FN risk warrants prevention [3]. Earlier European Organisation for Research and Treatment of Cancer guidance likewise established risk-adapted G-CSF prophylaxis as a core strategy for reducing chemotherapy-associated FN [4].

The main implementation problem is not simply whether guidance is available, but whether risk information is acted on consistently [5–7]. Breakdowns can occur at several points: risk assessment may be incomplete, high-risk patients may not receive prophylaxis in time, and multidisciplinary input or post-discharge follow-up may not be routinely integrated into the care pathway [5, 7–9]. These gaps can leave otherwise evidence-based recommendations unevenly applied in routine practice.

For this reason, CIN/FN management is not only a pharmacologic issue. It also depends on how information, responsibilities, and follow-up are organized across the care pathway. A more integrated approach brings risk assessment forward, links it to prevention and multidisciplinary decision-making, and extends monitoring beyond discharge [8–11].

Against this background, the China Anti-Cancer Association developed the Standardized Management and Discipline Development Program for Myelosuppression, guided by the principle of “assessment before treatment, prevention first, and routine implementation.” The program combined governance, information-system support, multidisciplinary teamwork, standard operating procedures, and closed-loop follow-up within a common framework that could be adapted locally.

The present study was undertaken after completion of the program to examine how care changed over time in routine practice. The primary objective was to describe program-level changes in risk assessment, prophylaxis, neutropenia-related outcomes, healthcare use, and follow-up. A secondary exploratory objective was to assess whether eight institutional implementation features were associated with specific process or outcome measures.

2 Methods

2.1 Study design and setting

After completion of the Myelosuppression Standardized Management Discipline Development Program, we conducted a multicenter retrospective observational evaluation using existing longitudinal aggregated hospital-level data. The national quality-improvement program was launched on March 2, 2024, and routine program data were collected through July 29, 2026. Ethics approval for the present retrospective research evaluation was granted on September 9, 2026; research-specific data assembly, cleaning, and statistical analysis began only after that approval. The study did not influence how any of the program components were implemented. The analytic unit was the hospital-month rather than the individual patient. Historical monthly indicators were assembled for 2 months before and up to 12 months after program implementation at each center and aligned to a common relative implementation timeline. The statistical evaluation was organized into two complementary levels: a primary program-

level longitudinal evaluation describing changes in process and outcome indicators after program implementation, followed by exploratory component-level analyses examining which of the eight institutional system-building characteristics were associated with specific indicators.

A total of 159 centers participated in the Myelosuppression Standardized Management Discipline Development Program. After program completion, 93 centers submitted retrospective institutional data for the present evaluation. Thirty-two centers were excluded because the submitted datasets had insufficient data completeness or internal logical inconsistencies that precluded reliable analysis, leaving 61 participating centers across 16 provincial-level regions in China. These 61 centers were nested within 54 unique hospitals because several hospitals contributed more than one participating clinical department. Hospital-level characteristics were therefore summarized using the 54 unique hospitals as the denominator, whereas implementation characteristics were assessed at the participating-center level. Among the 54 hospitals, 45 (83.3%) were Grade III Class A hospitals, 5 (9.3%) were Grade III Class B hospitals, 2 (3.7%) were Grade III hospitals without a specified class, and 2 (3.7%) were Grade II Class A hospitals. Hospital types included 44 general hospitals (81.5%), 5 specialized cancer hospitals (9.3%), 3 traditional Chinese medicine hospitals (5.6%), 1 integrated traditional Chinese and Western medicine hospital (1.9%), and 1 specialized chest hospital (1.9%). Because centers entered the program at different times and did not all contribute data through month 12, the number of centers contributing hospital-month outcome data varied over follow-up: 59 at pre-implementation month − 2, 59 at month − 1, and 60, 61, 60, 60, 59, 58, 55, 53, 50, 47, 44, and 41 at post-implementation months 1 through 12, respectively.

2.2 Myelosuppression Standardized Management Program and operational workflow

The program addressed chemotherapy-induced myelosuppression–related adverse events through multiple coordinated improvements spanning organizational management and clinical practice, rather than focusing on a single aspect of care. Its “Five Ones” framework comprised a hospital–department two-tier governance structure, an information system or platform, a stable multidisciplinary team (MDT), a standard operating procedure, and a closed-loop management pathway. These elements were translated into an eight-step workflow covering chemotherapy-order triggering, CIN/FN risk assessment, risk stratification, proactive MDT input for high-risk patients, team-based information sharing, ward-level risk-stratified management, bedside risk display and education, and post-discharge follow-up (Fig. 1).

Implementation was supported by staged training and periodic expert review. Review findings were fed back to participating centers so that gaps between the program standards and local practice could be addressed during implementation. In practice, centers differed in how quickly and how fully they adopted individual components, which allowed implementation maturity to be examined over time.

2.3 Institutional implementation characteristics evaluated in the component-level analysis

The retrospective analysis plan specified eight institutional implementation features: hospital information system (HIS) integration of CIN/FN risk assessment, data-driven Plan–Do–Check–Act (PDCA) management, automated absolute neutrophil count (ANC) critical-value alerts, pharmacist involvement, timing of MDT activation, risk-stratified patient education, a dedicated CIN/FN clinical consent/documentation form, and the post-discharge follow-up model. For descriptive implementation analyses, the distribution of each feature was summarized at pre-implementation month − 1 and post-implementation months 3, 6, and 12. The program-defined higher-maturity categories were mandatory HIS-based risk assessment, data-driven PDCA, automated ANC critical-value alerts, prophylactic pharmacist participation in MDT, proactive MDT initiation for high-risk patients, risk-stratified education, use of a dedicated CIN/FN clinical consent/documentation form, and intelligent closed-loop follow-up. Percentages were calculated using valid institutional responses for each feature at each time point; missing or invalid responses were excluded from the corresponding denominator. These implementation states had arisen during routine program delivery and were neither patient-level exposures nor investigator-assigned research interventions.

2.4 Outcome measures

Outcomes were grouped according to where they occurred in the care pathway. CIN/FN risk assessment represented the entry point; prophylaxis measures captured preventive action; CIN, FN, antimicrobial treatment, readmission, and hospital stay reflected downstream clinical burden and healthcare use; and follow-up and patient satisfaction reflected continuity after discharge. This grouping was used to support interpretation and did not imply a causal sequence.

2.5 Data collection and data protection

After program completion, participating centers retrospectively compiled monthly aggregate indicators from existing institutional quality-management records and information-system summaries using standardized program definitions. Numerator and denominator counts were extracted for rate outcomes where available; some historically retained indicators were available only as validated aggregate rates, and continuous outcomes were represented by hospital-level summary measures. In addition, we collected information on the implementation of each center’s management system at M − 1, M3, M6, and M12 to understand how these measures were progressively adopted over time. No patient names, medical-record numbers, identification numbers, dates of birth, individual treatment histories, or other directly identifiable patient-level information were included in the analytic dataset. Data extraction and central quality review were completed before the analytic data cutoff of July 29, 2026.

2.6 Statistical analysis

2.6.1 Descriptive longitudinal analysis

For the main program-level analysis, the month immediately before local implementation (M − 1) was used as baseline because it was the closest pre-implementation observation to M0. Baseline was compared with month 12 to summarize longer-term change. The baseline aggregate included 59 centers

and 16,437 patients receiving chemotherapy; the month-12 aggregate included 41 centers and 12,098 patients. Because the database contained aggregate counts and summary measures rather than linkable patient records, the two time-point patient populations were treated as independent samples. Fisher's exact test was used for rate outcomes with valid numerator and denominator counts, and two-sample t tests were used for continuous outcomes. Monthly plots were used to show the full trajectory. Month-12 estimates should therefore be interpreted as available-center results rather than complete follow-up of all 61 centers.

2.6.2 Generalized estimating equations

GEE models were used as an exploratory second-stage analysis to examine associations between each of the eight implementation features and 12 pre-specified process and outcome indicators (Online Resource 1). Proportion outcomes were modeled using event/trial counts with a binomial distribution and logit link and are reported as odds ratios (ORs) with 95% confidence intervals. Aggregate continuous outcomes — hospital length of stay and readmission percentage — were modeled with a normal distribution and identity link and are reported as absolute differences (days and percentage points, respectively). For each feature, the pre-implementation state served as the reference category.

Each model included the implementation status and a linear term for study month. Hospitals were specified as clusters to account for repeated monthly observations, with an exchangeable working correlation matrix; an independent structure was used for models in which the exchangeable structure did not yield valid covariance estimates. Robust (sandwich) standard errors remain valid under either structure. The eight features were modeled separately; reported associations should not be interpreted as mutually adjusted or independent effects. No adjustment for multiple comparisons was made, and all P values are nominal. For legibility, Fig. 5 displays only associations with nominal $P < 0.05$; all estimates are provided in Online Resource 1. This display rule affected presentation only and did not alter the underlying analyses.

2.6.3 Sensitivity analysis

As a sensitivity analysis, outcomes at M − 1 and M6 were compared using the Wilcoxon signed-rank test among hospitals with observations at both time points. Month 6 was chosen because center retention remained high at that point (58 centers contributing data, compared with 41 at month 12). This analysis was intended to check whether the direction of change seen in the main month-12 comparison was also apparent earlier, when loss of contributing centers was less pronounced.

2.6.4 Multiple testing

The component-level analyses were exploratory and no correction for multiple testing was applied. All P values are nominal and intended for trend assessment. They are reported to describe the strength and pattern of associations and should not be interpreted as confirmatory hypothesis tests.

2.7 Ethical considerations

The present retrospective study analyzed exclusively aggregated hospital-level data generated during the Myelosuppression Standardized Management Discipline Development Program and did not contain individual-level patient information, identifiable personal data, or biological material. The program was launched on March 2, 2024, routine program data were collected through July 29, 2026, and the retrospective research evaluation was approved on September 9, 2026, by the Ethics Review Committee of Shandong Cancer Hospital Affiliated to Shandong First Medical University (approval No. SDTHEC 202609003). Research-specific data assembly, cleaning, and statistical analysis began only after ethics approval. The study was conducted in accordance with the Declaration of Helsinki and applicable institutional requirements. The committee waived the requirement for individual informed consent because the evaluation used retrospective, aggregated, non-identifiable data.

3 Results

3.1 Participating-center context and progressive implementation maturation

Of the 159 centers participating in the program, 93 submitted retrospective institutional data; 32 were excluded because of insufficient data completeness or internal logical inconsistencies, leaving 61 participating centers from 54 hospitals across 16 provincial-level regions. Several hospitals contributed more than one participating clinical department. Among the 54 hospitals, 45 (83.3%) were Grade III Class A, 5 (9.3%) Grade III Class B, 2 (3.7%) Grade III without a specified class, and 2 (3.7%) Grade II Class A. General hospitals accounted for 44 (81.5%) of the 54 hospitals, followed by specialized cancer hospitals (5 [9.3%]), traditional Chinese medicine hospitals (3 [5.6%]), an integrated traditional Chinese and Western medicine hospital (1 [1.9%]), and a specialized chest hospital (1 [1.9%]). Monthly contributing centers were 59, 59, 60, 61, 60, 60, 59, 58, 55, 53, 50, 47, 44, and 41 from M−2 through M12, respectively.

Table 1. Characteristics of participating hospitals and baseline implementation context

Note: Hospital characteristics are based on 54 unique hospitals. The 61 participating centers included multiple clinical departments from some hospitals. Baseline implementation characteristics were measured at the center level; denominators vary according to valid responses for each measure.

Domain	Characteristic / program-defined category	Baseline value
Hospital grade	Grade III Class A	45/54 (83.3%)
	Grade III Class B	5/54 (9.3%)
	Grade III, class unspecified	2/54 (3.7%)
	Grade II Class A	2/54 (3.7%)
Hospital type	General hospital	44/54 (81.5%)
	Specialized cancer hospital	5/54 (9.3%)
	Traditional Chinese medicine hospital	3/54 (5.6%)
	Integrated traditional Chinese and Western medicine hospital	1/54 (1.9%)
	Specialized chest hospital	1/54 (1.9%)
Baseline implementation context (M−1)	Mandatory HIS-embedded CIN/FN risk assessment	6/57 (10.5%)
	Data-driven PDCA management	3/54 (5.6%)
	Automated ANC critical-value alert	23/57 (40.4%)
	Prophylactic pharmacist participation in MDT	3/55 (5.5%)
	Proactive MDT initiation for high-risk patients	2/54 (3.7%)
	Risk-stratified patient education	7/56 (12.5%)
	Dedicated CIN/FN clinical consent/documentation form	4/56 (7.1%)
	Intelligent closed-loop follow-up for moderate/high-risk patients	1/56 (1.8%)

Hospital grade and type are reported for the 54 unique hospitals. Baseline implementation percentages are center-level measures calculated using valid responses at M−1; therefore denominators vary across measures. HIS, hospital information system; PDCA, Plan–Do–Check–Act; ANC, absolute neutrophil count; MDT, multidisciplinary team.

Before program implementation, several more standardized and well-developed management practices had not yet been widely implemented across centers. Among centers with valid data, 10.5% had mandatory HIS-embedded CIN/FN risk assessment, 5.6% used data-driven PDCA, 5.5% involved pharmacists proactively in MDT, 3.7% initiated MDT proactively for high-risk patients, 12.5% provided

risk-stratified education, 7.1% used a dedicated CIN/FN clinical consent/documentation form, and 1.8% had intelligent closed-loop follow-up. Automated ANC critical-value alerts were more common at baseline and were available in 40.4% of centers. (Table 1).

Use of the higher-maturity categories increased across all eight implementation measures during follow-up (Figure 2). At month 12, among centers with valid data, 57.5% had mandatory HIS-based risk assessment, 77.5% used data-driven PDCA, 92.5% had automated ANC critical-value alerts, 72.5% involved pharmacists proactively in MDT, 80.0% initiated MDT proactively for high-risk patients, 95.0% provided risk-stratified patient education, and 67.5% used a dedicated CIN/FN clinical consent/documentation form. Intelligent closed-loop follow-up increased from 1.8% at baseline to 32.5% at month 12, but remained the least widely implemented of these more advanced practices. A further 60.0% of centers used information-assisted follow-up that had not yet achieved closed-loop management. Most of the change was already visible by months 3 and 6, consistent with gradual implementation rather than a single step-change at M0.

3.2 Changes in risk assessment, prophylaxis, and follow-up

CIN/FN risk-assessment coverage increased from 62.9% at baseline to 84.2% in the first post-implementation month and reached 98.0% by month 12 among centers with available data (baseline vs month 12, nominal $P<0.0001$). Because risk assessment was intended to inform subsequent decisions, this early increase suggests that centers first established a more consistent starting point for CIN/FN management before later elements of the pathway matured (Figure 3).

Preventive practice also changed over time. Overall primary prophylaxis increased from 25.4% to 42.2%, high-risk primary prophylaxis from 49.8% to 64.2%, and long-acting G-CSF primary prophylaxis from 41.1% to 56.7% (all nominal $P<0.0001$). High-risk total prophylaxis increased from 86.5% to 94.5%, while overall secondary prophylaxis increased from 18.5% to 25.3% (both nominal $P<0.0001$). Follow-up rose in parallel. Taken together, these trajectories show that changes occurred at several points in the management process rather than in a single measure alone (Figure 3; Table 2).

Table 2. Program-level comparison between baseline (pre-implementation month −1) and post-implementation month 12

Indicator	Baseline (M−1)	Month 12	Absolute change	Nominal P value
CIN/FN risk-assessment rate	10,344/16,437 (62.9%)	11,855/12,098 (98.0%)	+35.1 pp	<0.0001
Overall primary prophylaxis	4,178/16,437 (25.4%)	5,104/12,098 (42.2%)	+16.8 pp	<0.0001
Overall secondary prophylaxis	3,045/16,437 (18.5%)	3,065/12,098 (25.3%)	+6.8 pp	<0.0001
High-risk total prophylaxis	4,512/5,219 (86.5%)	5,298/5,604 (94.5%)	+8.1 pp	<0.0001
High-risk primary prophylaxis	2,599/5,219 (49.8%)	3,595/5,604 (64.2%)	+14.4 pp	<0.0001
Long-acting G-CSF primary prophylaxis	2,145/5,219 (41.1%)	3,180/5,604 (56.7%)	+15.6 pp	<0.0001
FN incidence	1,888/16,437 (11.5%)	365/12,098 (3.0%)	−8.5 pp	<0.0001
CIN incidence	33.6%	21.8%	−11.8 pp	<0.0001
Antimicrobial-treatment rate after CIN/FN	15.3%	5.6%	−9.7 pp	<0.0001
Myelosuppression-related readmission	8.6%	2.7%	−5.9 pp	<0.0001
Mean hospital length of stay	5.71 days	4.67 days	−1.04 days	0.0394
Follow-up rate	11,017/16,437 (67.0%)	11,584/12,098 (95.8%)	+28.7 pp	<0.0001
Patient satisfaction	94.4%	98.3%	+3.9 pp	<0.0001
Average hospitalization expenditure	CNY 6,450.7	CNY 5,384.5	−CNY 1,066.3	0.1151

Baseline was defined as pre-implementation month −1, the observation closest to program initiation (M0). Where integer numerator and denominator counts were available from the standardized aggregate dataset, values are shown as n/N (%); indicators historically retained only as aggregate rates or hospital-level summary measures are shown in their available form. The population receiving chemotherapy was 16,437 at baseline and 12,098 at month 12. Rate outcomes were compared using Fisher's exact test based on the available aggregated data at the two time points; continuous outcomes were compared using two-sample t tests. Month-12 values reflect centers with available month-12 data and therefore do not represent a complete 61-center cohort. All P values are nominal and are intended for exploratory interpretation rather than confirmatory inference. pp, percentage points; CNY, Chinese yuan.

3.3 Changes in neutropenia-related outcomes and healthcare use

As risk assessment, prevention, monitoring, and follow-up practices became more established, neutropenia-related events and the need for rescue treatment also declined. FN incidence decreased from 11.5% at baseline to 3.0% at month 12 and overall CIN incidence from 33.6% to 21.8% (both nominal P<0.0001). Antimicrobial treatment after CIN/FN decreased from 15.3% to 5.6% (nominal P<0.0001). The monthly indicators did not decline consistently and showed some fluctuation, but overall remained at relatively low levels toward the later stages of the program. (Figure 4). These changes were consistent with the program's intended management approach, but the available findings do not establish that increased preventive measures directly led to the reduction in CIN/FN.

Myelosuppression-related readmission decreased from 8.6% to 2.7% (nominal P<0.0001), and mean hospital length of stay fell from 5.71 to 4.67 days, a difference of 1.04 days (nominal P=0.0394). Lower rates were also observed across CIN severity categories among patients who received prophylaxis. Given the use of hospital-level aggregate data and the inability to adjust for patient-level case mix, these subgroup findings should be interpreted as descriptive patterns rather than as evidence of individual-level treatment effects.

Follow-up increased from 67.0% at baseline to 95.8% at month 12 (nominal P<0.0001), and patient satisfaction increased from 94.4% to 98.3% (nominal P<0.0001). Average hospitalization expenditure decreased from CNY 6,450.7 to CNY 5,384.5, a difference of CNY 1,066.3, but this was not statistically significant (nominal P=0.1151). Accordingly, the changes observed following program implementation extended beyond preventive practices and neutropenia-related outcomes to encompass healthcare resource utilization and continuity of post-discharge care. (Table 2).

3.4 Month-6 sensitivity analysis

The month-12 analysis included 41 contributing centers, so we also examined an earlier time point with greater center retention. At month 6, 58 centers were still contributing data. In centers with paired M−1 and M6 observations, Wilcoxon analyses showed changes in the same general direction for CIN/FN risk assessment, overall primary prophylaxis, FN, CIN, antimicrobial treatment, follow-up, high-risk primary prophylaxis, high-risk total prophylaxis, myelosuppression-related readmission, and hospital length of stay (Table 3). This finding reduces, to some extent, the possibility that the M12 results were driven entirely by changes in the composition of participating centers, although such an influence cannot be fully excluded.

Table 3. Paired Wilcoxon sensitivity analysis: pre-implementation month −1 versus post-implementation month 6

Outcome	Median paired difference (Q1, Q3), pp unless noted	P value	Direction
Overall CIN/FN risk assessment	27.0 (6.0, 49.0)	<0.0001	Increase
Overall primary prophylaxis	10.0 (2.0, 26.0)	<0.0001	Increase
Overall secondary prophylaxis	3.0 (−3.0, 14.0)	0.0083	Increase
FN incidence	−2.0 (−4.0, 0.0)	<0.0001	Decrease
CIN incidence	−6.0 (−14.0, 1.0)	0.0002	Decrease
Antimicrobial-treatment rate	−2.0 (−7.0, 0.0)	0.0066	Decrease
Follow-up rate	11.0 (0.0, 27.0)	<0.0001	Increase
High-risk primary prophylaxis	12.0 (−1.0, 34.0)	<0.0001	Increase
High-risk secondary prophylaxis	−2.0 (−15.0, 10.0)	0.3251	No clear difference
High-risk total prophylaxis	6.0 (0.0, 27.0)	<0.0001	Increase
Myelosuppression-related readmission	−1.75 (−3.70, −0.50)	<0.0001	Decrease
Hospital length of stay	−0.30 (−1.40, 0.00) days	0.0002	Decrease

P values are nominal. Post-implementation month 6 was selected as an earlier paired sensitivity time point because center retention was substantially higher at month 6 (58 contributing centers) than at month 12 (41 contributing centers). The Wilcoxon signed-rank test used hospitals with data available at both M−1 and M6 as paired units. Rate differences are reported in percentage points; hospital length of stay is reported in days. This analysis complements, rather than replaces, the primary baseline-to-month-12 available-center comparison.

3.5 Associations between implementation features and care processes or outcomes

The exploratory GEE analyses were primarily used to assess whether different management measures were associated with different aspects of care, including risk assessment, prevention, follow-up, and clinical outcomes. No single feature was associated with the full set of changes. Mandatory HIS-based assessment was strongly associated with completion of CIN/FN risk assessment (OR 4.48, 95% CI 1.87–10.76; nominal P=0.0008), and risk-stratified education was also associated with assessment completion (OR 3.36, 95% CI 1.85–6.13; nominal P<0.0001). Data-driven PDCA was associated with overall primary prophylaxis (OR 1.93, 95% CI 1.06–3.50; nominal P=0.0308) and with high-risk total prophylaxis (OR 4.37, 95% CI 2.08–9.17; nominal P<0.0001).

Associations with downstream outcomes differed. Intelligent closed-loop follow-up was associated with lower FN incidence (OR 0.55, 95% CI 0.40–0.77; nominal P=0.0004). Proactive MDT activation for high-risk patients and preventive pharmacist participation were associated with lower readmission (−3.42 percentage points, 95% CI −6.38 to −0.47; nominal P=0.0232, and −2.97 percentage points, 95% CI −5.66 to −0.27; nominal P=0.0312, respectively). Figure 5 shows representative associations, with full component-by-outcome estimates provided in Online Resource 1.

4 Discussion

4.1 Key findings

The main finding of this study was the broad change in how participating centers organized CIN/FN management after program implementation. Before the program began, many standardized and well-developed management practices were not yet widely implemented. Over the following months, the use of information-system support, PDCA, multidisciplinary collaboration, patient education, dedicated informed consent documentation, and follow-up gradually increased. At the same time, risk assessment became more routine, preventive measures were used more frequently, neutropenia-related events and rescue treatment declined, and follow-up became more complete. Compared with any single nominal P value, the consistent direction of change across implementation, process, and outcome measures provides a more informative picture of the overall changes observed after program implementation.

The GEE analyses further helped clarify how different management measures may relate to different stages of care. Electronic risk assessment was mainly associated with risk identification, while PDCA and risk-stratified education were more closely related to preventive processes. Intelligent follow-up was associated with FN outcomes, whereas proactive MDT involvement and pharmacist participation were more closely related to readmission. Overall, these findings suggest that multiple management measures may contribute at different stages of care, rather than any single intervention accounting for the overall changes observed with the program.

4.2 Risk identification as the first step in standardized management

FN risk assessment provides an important basis for preventive decision-making [1–5], but in routine clinical practice this step is not always performed consistently. Following program implementation, the proportion of patients undergoing risk assessment increased substantially, suggesting that participating centers increasingly incorporated risk identification into routine care. This is consistent with previous studies showing that computerized tools can improve risk documentation and adherence to guideline-based management [12, 13]. In our exploratory analysis, centers using mandatory HIS-based electronic assessment were more likely to complete CIN/FN risk assessment (OR 4.48), further supporting the potential role of information systems in the risk-identification process.

However, completing a risk assessment does not mean that the entire management process has been completed. We did not observe an equally clear association between HIS integration and the incidence of FN or CIN. Electronic systems can help clinical teams identify patients who require assessment and make risk information more accessible, but whether preventive measures are actually implemented, patient education is completed, multidisciplinary collaboration is initiated, and post-discharge follow-up is carried out still depends on other parts of the management process. This may help explain why the clinical effects of electronic decision support have varied across healthcare settings [6]. Digital tools may therefore be most effective when they function as one component of a broader management pathway rather than as a stand-alone intervention intended to improve clinical outcomes.

4.3 From reactive management to risk-based proactive prevention

An important change introduced by the program was the earlier timing of CIN/FN management. Traditionally, supportive care was often intensified only after neutropenia or fever had already occurred. In contrast, the program emphasized risk assessment before treatment, followed by risk-adapted preventive measures and earlier MDT involvement for high-risk patients. After implementation, the overall primary prophylaxis rate increased from 25.4% to 42.2%, primary prophylaxis among high-risk patients increased from 49.8% to 64.2%, and total prophylaxis in high-risk patients reached 94.5%. The increase in primary prophylaxis with long-acting G-CSF among high-risk patients further reflected a shift in management from post-event treatment toward earlier prevention.

At the same time, the incidence of FN decreased to 3.0%, CIN incidence decreased to 21.8%, and antimicrobial treatment after CIN/FN decreased to 5.6%. These changes were directionally consistent with previous evidence that appropriate G-CSF prophylaxis can reduce the risk of FN [5, 14]. Complete patient-level information was not available, limiting our ability to account for chemotherapy regimens, baseline patient risk, and other factors that may have changed over time. A more appropriate interpretation is that, as the timing of intervention moved earlier and preventive measures were used more widely, the clinical burden associated with neutropenia also declined. These findings therefore reflect concurrent favorable changes across multiple indicators during program implementation rather than a comparative estimate of the efficacy of any specific drug.

4.4 Continuous quality improvement and patient education are important components of standardized management

Once risk has been identified, the next challenge is to ensure that this information is translated into subsequent management. Clinical orders or information-system prompts alone are not sufficient to complete this process. Risk-stratified patient education, data-driven PDCA, and dedicated informed consent documentation were associated with multiple process measures, although none represents a pharmacologic intervention. Risk-stratified education can help patients and caregivers better understand which symptoms to monitor, when to seek medical attention, and how follow-up should be carried out after discharge. Dedicated informed consent documentation further supports this process by recording

the communication between clinicians and patients regarding the identified risk, available preventive options, and relevant self-care requirements. Such documentation provides a basis for reviewing whether risk information has been adequately communicated and whether it has informed patients' preventive decisions. It may therefore facilitate informed acceptance of G-CSF prophylaxis and strengthen self-protective behaviors, including symptom monitoring, timely reporting, and adherence to follow-up. The associations of these components with risk assessment, prevention, and follow-up may reflect a more developed management environment in which risk information is not only documented but also effectively communicated and translated into action by both clinical teams and patients.

PDCA, in contrast, operates primarily at the organizational and process levels. Even when standardized procedures are in place, gaps in implementation may be difficult to identify without continuous data monitoring. Through repeated measurement, feedback, and adjustment, centers can progressively narrow the gap between recommended practice and actual implementation. The staged training and periodic expert reviews incorporated into the program provided an additional feedback mechanism. These reviews were not intended solely as end-of-program evaluations, but were also used to identify local implementation gaps and guide subsequent improvements in management. Among centers with valid data, the proportion using data-driven PDCA increased from 5.6% at baseline to 77.5% at M12. The GEE analysis also showed that data-driven PDCA was associated with a higher rate of total prophylaxis among high-risk patients. Together, these findings suggest that standardized management is more appropriately viewed as a continuous process of monitoring, feedback, improvement, and reassessment rather than as the one-time introduction of an SOP.

4.5 Closed-loop follow-up extends CIN/FN management beyond discharge

CIN/FN management does not end when the patient leaves the hospital. The neutropenic nadir and episodes of FN may occur between clinical visits, when patients are no longer under direct observation by the inpatient team. Continued monitoring and timely communication after discharge are therefore important components of the overall management process. By M12, the follow-up rate had increased from 67.0% to 95.8%, representing one of the more prominent changes observed during the program. After adjustment for time trends, exploratory GEE analysis also showed that intelligent closed-loop follow-up was associated with a lower incidence of FN. Previous randomized studies in oncology have similarly shown that electronic symptom monitoring and web-based follow-up can facilitate earlier symptom detection and may reduce acute healthcare use or support more timely clinical intervention [10, 15].

Within this program, closed-loop follow-up may have helped patients complete scheduled laboratory monitoring, recognize fever or infection earlier, and communicate with the clinical team in time for further management. However, this association does not demonstrate that intelligent follow-up itself reduced the incidence of FN. Centers capable of implementing intelligent closed-loop follow-up may also have had stronger multidisciplinary teams, more developed information systems, and better supportive-

care infrastructure. A more appropriate interpretation is that continuity of care after discharge represents an important component of standardized CIN/FN management and should be closely integrated with pretreatment risk assessment and preventive measures.

4.6 Multidisciplinary collaboration may be associated with improved healthcare resource use

Following program implementation, the rate of myelosuppression-related readmission decreased from 8.6% to 2.7%, and the mean length of hospital stay was shortened by approximately 1 day. In the exploratory GEE analyses, proactive MDT initiation and preventive pharmacist involvement were both associated with lower readmission rates. Previous oncology studies have also suggested that pharmacist involvement and interdisciplinary supportive-care models may improve medication management, symptom control, treatment adherence, and other aspects of care, although the findings across studies have been heterogeneous [11, 16].

From a clinical perspective, these associations are plausible. Preventing avoidable deterioration often requires coordination among physicians, pharmacists, nurses, and other members of the care team, with effective integration across chemotherapy planning, supportive treatment, infection management, laboratory monitoring, and post-discharge follow-up. However, these findings remain associative and do not establish that MDT involvement or pharmacist participation directly reduced readmissions.

Mean hospitalization costs also decreased numerically, although the difference was not statistically significant. Previous economic studies from China have suggested that FN prevention may help reduce subsequent healthcare costs [17], but the present study was not designed as a cost-effectiveness analysis. The economic value of system-based management therefore requires further evaluation in prospective studies that consider the costs of information infrastructure, team-based care, and follow-up alongside potential reductions in complications, hospitalizations, and length of stay.

4.7 A system-based model aligned with the principles of integrative oncology

Taken together, the findings suggest that different management measures may contribute at different stages of CIN/FN care. Information systems can support timely risk identification; patient education and PDCA can help translate risk information into concrete preventive and management actions; MDT involvement and pharmacist participation can support complex clinical decision-making; and closed-loop follow-up can help maintain continuity of care after discharge. These findings suggest that CIN/FN management is unlikely to depend on any single measure, but rather on the coordination of multiple components. This is also consistent with implementation science frameworks, which emphasize that the translation of evidence-based practices into routine care is shaped by the intervention itself, the organizational context, the implementation process, and the people involved [18, 19].

This perspective is also aligned with holistic integrative oncology. Supportive care should not be viewed as an add-on to anticancer treatment, but as an integral part of the overall treatment process. The management sequence observed in this study—from risk identification and preventive decision-making to multidisciplinary collaboration, patient education, post-discharge follow-up, and data-driven feedback and improvement—illustrates how CIN/FN management can be integrated throughout the patient journey. In a national multicenter setting, the key is not for every center to adopt exactly the same technology or team structure, but to ensure that each part of the management process is effectively connected to the next, forming a continuous and coordinated system of care.

4.8 Strengths

This study has several notable strengths. It included 61 centers across 16 provincial-level regions in China, allowing the standardized management program to be evaluated across diverse clinical settings rather than reflecting the experience of a single institution. The study also captured how the management system developed over time, rather than focusing only on before-and-after changes in clinical indicators. Eight institutional management measures were assessed at baseline and at M3, M6, and M12 and were considered alongside concurrent patient management indicators. This made it possible to observe how the program evolved from initial implementation toward more complete adoption. For the statistical analyses, hospital-month was used as the unit of analysis. The GEE models accounted for repeated observations within hospitals and adjusted for linear time trends. Importantly, the study distinguished between two related but different questions: whether management processes and clinical outcomes changed over time after program implementation, and which specific management measures were associated with particular process indicators or clinical outcomes. This approach allowed the findings to be interpreted at both the overall program level and the level of individual management components.

4.9 Limitations

This study also has several limitations that should be considered. Because of the retrospective, nonrandomized design and the absence of a concurrent external control group, the changes observed before and after program implementation cannot be attributed entirely to the program itself. The implementation measures were not assigned for research purposes, and contemporaneous changes in guideline awareness, chemotherapy practice, supportive-care use, and other local quality-improvement efforts may also have influenced the observed temporal trends.

Implementation measures were also unlikely to be independent within the same center and may have been adopted together as overall management capacity improved. For example, centers with more developed information systems may also have had more established MDT processes, patient education, and follow-up systems. Accordingly, the findings from the exploratory GEE models, in which the eight implementation features were examined separately, should be interpreted as associations between specific implementation features and corresponding processes or outcomes rather than as independent or causal effects of any single component. The GEE models accounted for repeated observations within

hospitals and adjusted for linear time trends, but they could not fully control for unmeasured center-level differences or disentangle the contributions of multiple management measures implemented concurrently.

The number of centers contributing data decreased over time. In the primary comparison, 59 centers contributed data at M − 1 and 41 at M12, while 40 centers provided valid data for all eight implementation measures shown in Fig. 2 at M12. The differences observed at M12 may therefore reflect both within-center changes over time and changes in the composition of contributing centers. To assess this issue, we performed a paired sensitivity analysis from M − 1 to M6; when 58 centers still contributed outcome data at M6, multiple indicators showed changes in the same direction as in the primary analysis. This reduces, to some extent, the possibility that the M12 findings were explained entirely by changes in center composition.

5 Conclusion

In this multicenter retrospective evaluation, multiple aspects of CIN/FN management changed following implementation of the Myelosuppression Standardized Management Discipline Development Program. Risk assessment became increasingly routine, the use of preventive measures increased, neutropenia-related events and rescue treatment declined, and follow-up became more complete. Overall, CIN/FN management shifted from predominantly reactive care after events occurred toward a more proactive and continuous model of supportive care.

Exploratory analyses further suggested that different management measures were associated with different stages of the care process. Information-system support, PDCA, patient education, MDT involvement, pharmacist participation, and follow-up were each associated with different process indicators or clinical outcomes. These findings support viewing CIN/FN management as a multidisciplinary, longitudinal component of cancer care that spans the treatment course and extends beyond hospital discharge, rather than as a process driven by any single intervention. Given the retrospective, nonrandomized design and the use of hospital-level aggregate data, these findings should be interpreted as associations observed during program implementation and require further validation in studies with concurrent controls and patient-level data.

Declarations

Acknowledgments

The program benefited from the advice provided by its Advisory Committee members, Binghe Xu, Jinming Yu, and Yuquan Wei, and from the guidance provided by its Steering Committee members, Beihua Kong, Suxia Luo, Hongming Pan, Jun Liang, Xianglin Yuan, Zhao Yan, Li Zhang, and Weili Zhao.

The contributions of all participating institutions and clinical teams to the Myelosuppression Standardized Management Discipline Development Program and to the retrospective provision of

institutional quality-management data for this study are gratefully acknowledged.In addition to the named authors, the writing committee included the following members of the CACA Myelosuppression Standardized Management Working Group (CMMW)

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Consent for publication

Not applicable. The manuscript contains no identifiable individual participant information.

Data availability

The datasets generated during and analyzed during the current study are not publicly available due to applicable privacy laws but are available from the corresponding author on reasonable request.

Funding

This work was supported by the Myelosuppression Standardized Management Program Fund.

Competing interests

The authors declare that they have no competing interests.

Author contributions

Zhao Yan, Bo Liu, Ji-Yan Liu, and Jing Liang contributed equally and share first authorship. All authors contributed to the project and the manuscript, reviewed the manuscript, and approved the final version.

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Figures

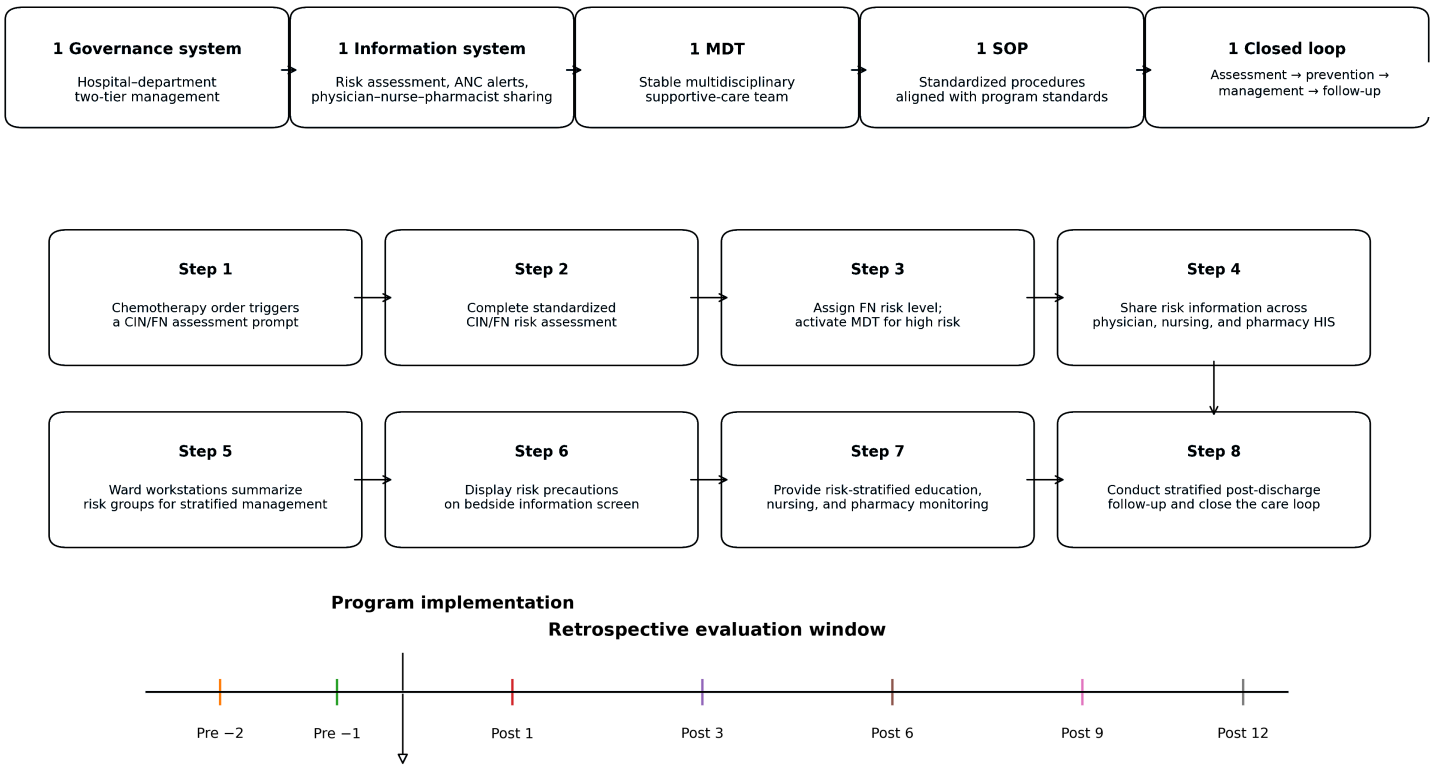

Figure 1

Program architecture, operational pathway, and retrospective evaluation design. The “Five Ones” architecture established governance, information, multidisciplinary, procedural, and closed-loop infrastructure, which was operationalized as an eight-step pathway from chemotherapy-order prompting

and CIN/FN risk assessment to post-discharge follow-up. The national program was launched on March 2, 2024; for analysis, M0 was aligned to each center's own implementation anchor. Historical data included 2 pre-implementation months and up to 12 post-implementation months and were collected through July 29, 2026. ANC, absolute neutrophil count; MDT, multidisciplinary team; SOP, standard operating procedure

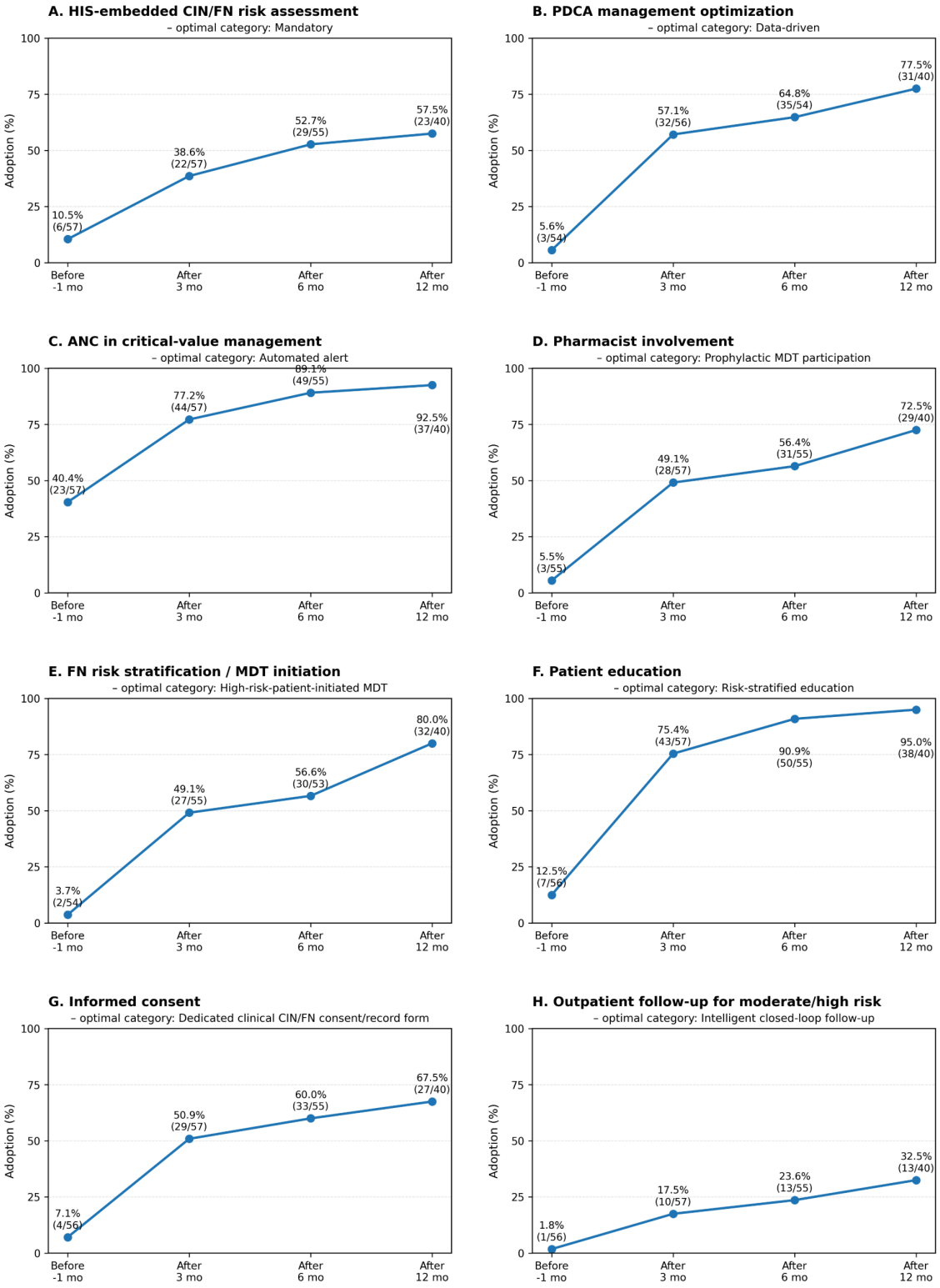

Figure 2

Changes over time in the implementation of eight institutional management measures. Percentages were calculated using centers with valid data at each time point. For each measure, the numerator shows the number of centers that reached the predefined higher-maturity level, and the denominator shows the number of centers with valid data. Implementation was assessed at pre-implementation month −1 and at months 3, 6, and 12 after implementation. The amount of available data varied across measures and time points; at month 12, valid data were available from 40 centers for all eight measures. HIS, hospital information system; CIN, chemotherapy-induced neutropenia; FN, febrile neutropenia; PDCA, Plan–Do–Check–Act; ANC, absolute neutrophil count; MDT, multidisciplinary team. Panel g refers to a dedicated CIN/FN clinical consent/documentation form used in routine care and does not refer to research informed consent

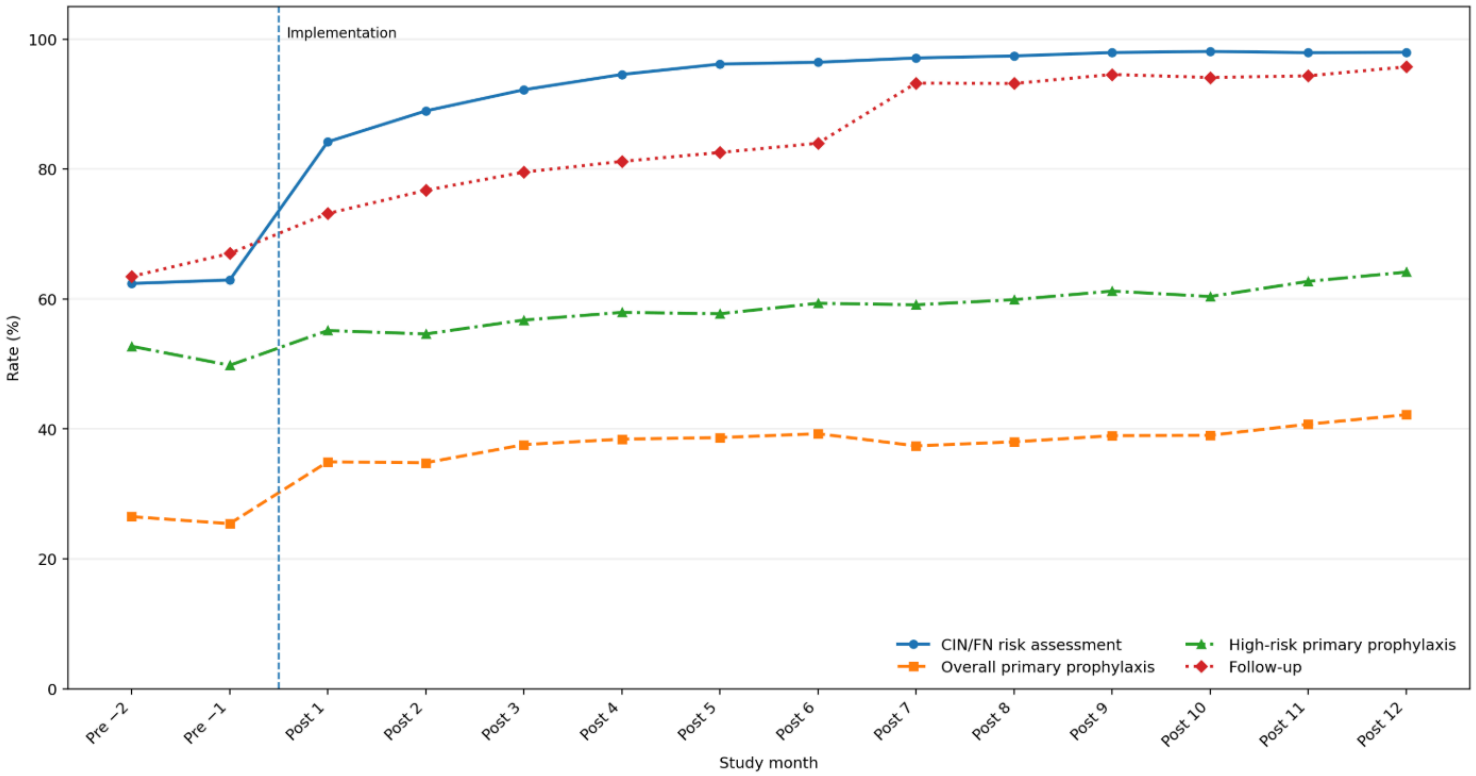

Figure 3

Longitudinal transition from risk recognition to proactive prevention and follow-up. Monthly rates are shown for CIN/FN risk assessment, overall primary prophylaxis, high-risk primary prophylaxis, and post-discharge follow-up across 2 pre-implementation months and up to 12 post-implementation months. The numbers of contributing centers at M−2, M−1, and M1 through M12 were 59, 59, 60, 61, 60, 60, 59, 58, 55, 53, 50, 47, 44, and 41, respectively. Later monthly estimates therefore represent progressively smaller available-center subsets

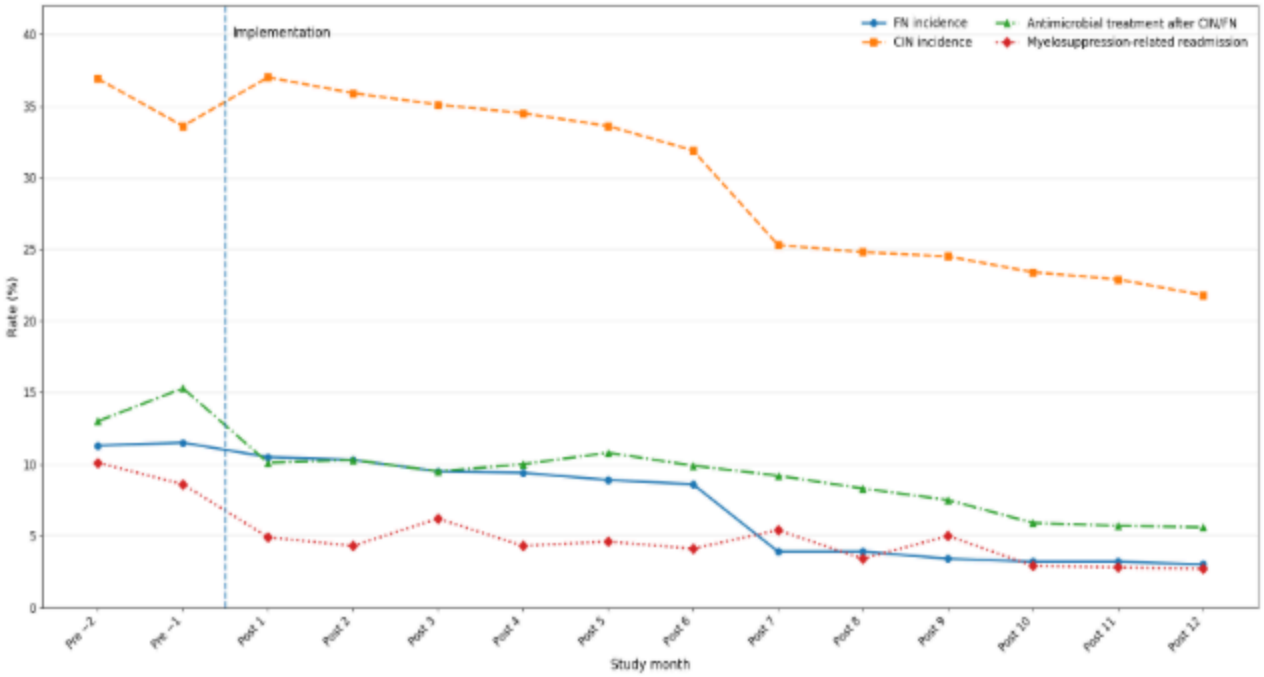

Figure 4

Longitudinal changes in neutropenia-related clinical burden and downstream care. Monthly rates are shown for FN incidence, CIN incidence, antimicrobial treatment after CIN/FN, and myelosuppression-related readmission across 2 pre-implementation months and up to 12 post-implementation months. The numbers of contributing centers at M−2, M−1, and M1 through M12 were 59, 59, 60, 61, 60, 60, 59, 58, 55, 53, 50, 47, 44, and 41, respectively. Later monthly estimates therefore represent progressively smaller available-center subsets

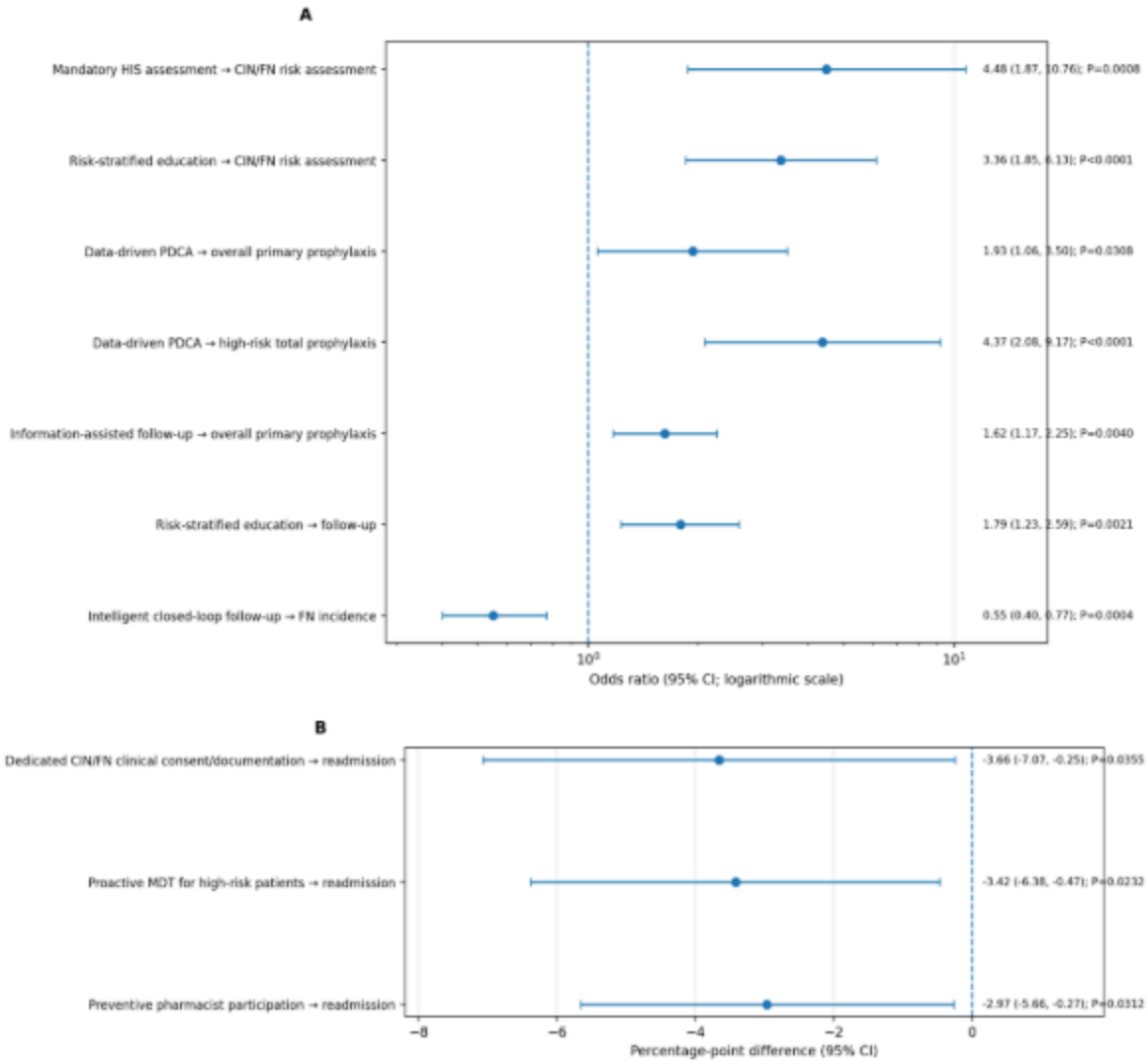

Figure 5

Representative exploratory associations between system-building characteristics and outcomes in GEE models, mapped to different stages of the CIN/FN care pathway. Panel a shows selected proportion outcomes as odds ratios (ORs) with 95% confidence intervals on a logarithmic scale; the vertical reference line is OR=1. Panel b shows selected associations with myelosuppression-related readmission as percentage-point differences with 95% confidence intervals; the vertical reference line is 0. Only component–outcome associations with nominal P<0.05 are displayed for legibility; complete model estimates, including non-associated results, are provided in Online Resource 1. Models adjusted for a linear temporal trend and accounted for repeated monthly observations within hospitals. All P values are nominal because the component-level analyses were exploratory

Supplementary Files

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

- OnlineResource1.docx