Journal of Cancer Research and Practice

journal homepage: https://journals.lww.com/jcrp

Original Article

Impact of Early versus Delayed G-CSF Administration on Clinical Outcomes in Chemotherapy-induced Neutropenia: A Propensity Score-matching Cohort Study

Hsieh-Ting Lin[1], Lun-Wei Chiou[2]*, Nei-Min Chu[3], Chi-Feng Chung[1], Chu-Yun Chen[1], Peng-Yu Chen[1], Hsiao-Hsiang Cheng[1]

[1]Department of Medical Oncology, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan
[2]Department of Hematopoietic Stem Cell Transplantation and Cell Therapy, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan
[3]Dean's Office, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan

Abstract

Background: Chemotherapy-induced neutropenia is a significant complication in cancer treatment, increasing the risk of infection and treatment delay. Granulocyte-colony stimulating factor (G-CSF) is used to treat and prevent neutropenia; however, the optimal timing of administration remains uncertain. This study evaluates the impact of early (48–72 h postchemotherapy) versus delayed G-CSF administration on clinical outcomes. **Materials and Methods:** This retrospective cohort study was conducted at Koo Foundation Sun Yat-Sen Cancer Center and included patients with early-stage breast cancer who received adjuvant chemotherapy between 2013 and 2023. All patients received standardized adjuvant AC → T: doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² (four 21-day cycles), followed by docetaxel 60 mg/m² over 60 min (four 21-day cycles). The patients were categorized according to the timing of first G-CSF administration in each chemotherapy cycle: early (48–72 h postchemotherapy; days 3–5) versus delayed (>72 h). Propensity score matching was applied to balance baseline characteristics, creating a matched cohort (n = 236). The primary outcomes were febrile neutropenia and grade 2–3 neutropenia. Kaplan–Meier survival analysis and Cox proportional hazards models were used to assess differences in clinical outcomes. **Results:** Early G-CSF administration significantly improved event-free survival (hazard ratio [HR] = 0.46, 95% confidence interval [CI]: 0.31–0.67, $P < 0.001$), fever-free survival (HR = 0.36, 95% CI: 0.20–0.67, $P = 0.001$), and neutropenia-free survival (HR = 0.53, 95% CI: 0.35–0.81, $P = 0.003$). Sensitivity analyses confirmed the robustness of these findings. **Conclusion:** Early G-CSF administration significantly improved clinical outcomes in chemotherapy-induced neutropenia. Future prospective studies should refine patient selection for tailored G-CSF timing strategies.

Keywords: Chemotherapy-induced neutropenia, delayed administration, early administration, febrile neutropenia, granulocyte-colony stimulating factor, hematologic recovery, infection risk, propensity score matching, survival analysis

Address for correspondence: Dr. Lun-Wei Chiou, Department of Hematopoietic Stem Cell Transplantation and Cell Therapy, Koo Foundation Sun Yat-Sen Cancer Center, No. 125, Lide Road, Beitou District, Taipei 11259, Taiwan.
E-mail: jefflwchiou@kfsyscc.org

Submitted: 28-Jul-2025 **Revised:** 15-Sep-2025
Accepted: 09-Nov-2025 **Published:** 10-Apr-2026

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jcrp

DOI: 10.4103/ejcrp.eJCRP-D-25-00039

How to cite this article: Lin HT, Chiou LW, Chu NM, Chung CF, Chen CY, Chen PY, *et al*. Impact of early versus delayed G-CSF administration on clinical outcomes in chemotherapy-induced neutropenia: A propensity score-matching cohort study. J Cancer Res Pract 2026;13:59-66.

Introduction

Chemotherapy-induced neutropenia is one of the most critical complications arising from cancer treatment, characterized by a reduction in neutrophil levels that increases the risk of severe infection and prolonged hospitalization. To address this clinical challenge, granulocyte-colony stimulating factor (G-CSF) plays a pivotal role in promoting neutrophil recovery by stimulating bone marrow activity. However, while its administration is largely supported by clinical guidelines, the optimal timing remains unclear. Current recommendations advocate for initiating G-CSF within 24–72 h after chemotherapy, however, variability in timing and diverse outcomes observed across studies suggest the need for refined guidance backed by real-world evidence.

Preventing neutropenia through timely intervention is of paramount importance.[1] G-CSF is endorsed by the National Comprehensive Cancer Network and American Society of Clinical Oncology as an effective means to reduce both the incidence and duration of neutropenia and febrile neutropenia (FN) (2022). Previous studies have demonstrated that G-CSF prophylaxis can reduce neutropenia-related hospitalizations, antibiotic exposure, and treatment interruptions, thereby enabling patients to maintain chemotherapy dose intensity and optimize survival outcomes.[2] Nevertheless, the clinical benefits achieved by G-CSF administration depend heavily on its timing after chemotherapy, and thus, further studies are needed to clarify the optimal timing of administration.

The existing literature suggests that the timing of G-CSF administration, whether early (≤24 h postchemotherapy) or delayed (≥48 h postchemotherapy), has a marked influence on clinical efficacy. A previous study hypothesized that administering G-CSF during the regenerative phase of hematopoiesis – when progenitor cells are actively recovering – may align with the biological processes underpinning neutrophil proliferation.[3] This hypothesis supports early G-CSF administration but is tempered by concerns about potential adverse effects and reduced efficacy when done prematurely.

Evidence from randomized trials and retrospective analyses has shown mixed conclusions. Some research supports the early initiation of G-CSF due to a reduction in FN incidence without compromising the time of neutrophil count recovery. For example, one study concluded that initiating G-CSF within the first 24 h postchemotherapy decreased the likelihood of FN and reduced hospitalization duration.[3] Conversely, another study suggested that delayed administration achieved comparable outcomes while offering advantages such as reduced need for platelet transfusion and improved patient stabilization.[4] These inconsistencies suggest that the efficacy depends on individual patient condition and treatment protocol, making uniform recommendations difficult.

Real-world data show that the timing of administration remains varied across clinical practices. According to a meta-analysis of clinical studies, G-CSF was often administered at inconsistent time frames ranging from 24 to 72 h postchemotherapy, depending on physician preference, patient risk profile, and institutional guidelines.[5] Disparities in timing have been associated with differing rates of FN and delayed chemotherapy.[2]

Of note, observational studies have underscored the effectiveness of prolonged G-CSF use in reducing hospitalization rates. This suggests that extended administration of at least 7 days can optimize neutrophil engraftment when initiated appropriately after chemotherapy. High-quality scoping reviews have demonstrated fewer hospitalization days and FN-related complications with the use of extended prophylaxis; however, logistical and financial constraints often limit the extended use of G-CSF in practical settings.

These inconsistent findings advocate for a more tailored and evidence-based approach to determine the ideal timing of G-CSF administration. Standardized timing may be insufficient to address the nuanced needs of chemotherapy patients, including those who are older or have comorbidities and may require modified schedules (2022). Guidelines must incorporate risk stratification tools accounting for patient-specific factors such as chemotherapy regimen intensity, prior FN episodes, and overall clinical frailty.

In this study, we defined early G-CSF as 48–72 h postchemotherapy, reflecting institutional standard practice intended to avoid administration during peak cytotoxic exposure while preceding the typical neutrophil nadir. This window also aligns with pragmatic considerations within Taiwan's reimbursement framework for secondary prophylaxis. The aim of the study was to evaluate the impact of early (48–72 h postchemotherapy) versus delayed (>72 h) G-CSF administration on clinical outcomes in patients treated for early-stage breast cancer.

Materials and Methods

Study design and population

This retrospective cohort study included patients diagnosed with early-stage breast cancer who underwent surgery and adjuvant chemotherapy at Koo Foundation Sun Yat-Sen Cancer Center between January 1, 2013, and December 31, 2023. Patients diagnosed with Stage II or III breast cancer at our institution who underwent surgical intervention followed by adjuvant therapy for operable node-positive or triple-negative breast cancer were included in this study. All patients received standardized adjuvant AC → T: doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² (four 21-day cycles), followed by docetaxel 60 mg/m² over 60 min (four 21-day cycles).[6] Patients who had received G-CSF at any point within 180 days after the start of chemotherapy were considered to have received secondary prophylaxis. Patients who did not complete the abovementioned regimen or had incomplete data regarding G-CSF administration were excluded from the analysis.

The study protocol was reviewed and approved by the Institutional Review Board of Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan (No. 20250801A; Date: July 20, 2025). As a retrospective study using de-identified data, the requirement for informed consent was waived by the IRB. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Definitions and exposure variables

The patients were categorized according to the timing of the first G-CSF administration following chemotherapy. Early G-CSF administration was defined as the first dose administered 48–72 h after the start (Day 1) of a chemotherapy cycle. Delayed G-CSF administration was defined as the first dose administered >72 h after the start of a cycle. The timing of G-CSF administration was calculated relative to the 1st day of each chemotherapy cycle. The timing data were collected retrospectively through electronic medical records, which provided detailed documentation of chemotherapy start dates, time of G-CSF administration, and patient-specific treatment cycles. The electronic medical records were reviewed to ensure accurate data extraction, and cross-referencing with nursing notes and medication logs was performed to validate timing accuracy.

Importantly, under the Taiwan National Health Insurance (NHI) reimbursement policy, G-CSF could not be prescribed as true primary prophylaxis, and the patients were eligible for G-CSF only after experiencing a prior neutropenic fever or significant neutropenia event with the same regimen. Thus, all administrations in this cohort should be considered secondary prophylaxis (reactive use) rather than primary prophylaxis. Our comparisons, therefore, reflect differences in early versus delayed timing within a reactive/secondary prophylactic framework.

The primary endpoints were fever-free survival (FFS) and neutropenia-free survival (NFS). Because all G-CSF administrations in this cohort followed the NHI reimbursement policy (i.e. reactive/secondary prophylaxis), Day 1 was defined as the date of first G-CSF administration rather than the start of chemotherapy. FFS was defined as the time from Day 1 to the first documented fever (oral temperature ≥38.3°C). NFS was defined as the time from Day 1 to the first episode of neutropenia, defined as an absolute neutrophil count (ANC) <1000/μL. Severe neutropenia was defined as grade 4 (ANC <500/μL). Patients were censored at death, last follow-up, or at 360 days, whichever came first. Each endpoint was analyzed as time-to-first event per patient; recurrent events were not double counted in the primary analysis. The secondary outcomes were the duration of neutropenia (from ANC <1000/μL until recovery ≥1000/μL), the need for hospitalization and length of stay due to FN, and chemotherapy dose modifications in subsequent cycles.

Baseline comparisons

Baseline differences between the early and nonearly G-CSF groups were assessed using appropriate comparative tests. For continuous variables with normal distribution, independent two-sample *t*-tests were used to determine statistical significance. When the data were skewed or nonnormally distributed, the Mann–Whitney *U*-test was used as a nonparametric alternative.[7] For categorical variables, the Chi-square test was used to compare proportions when expected cell frequencies met assumptions, and Fisher's exact test was used for comparisons involving small sample sizes to ensure statistical validity.[8]

Propensity score matching

To address potential confounding factors and minimize biases arising from differences in baseline characteristics, propensity score matching (PSM) was implemented.[9] This approach aimed to balance the covariates between the early and nonearly G-CSF administration groups, creating a pseudo-randomized setting. Propensity scores were derived through a logistic regression model, with the inclusion of clinically relevant covariates such as patient age, tumor stage, chemotherapy dose intensity, baseline ANC, performance status, and comorbidities.

Matching algorithm and criteria

Matching was performed using a 1:1 nearest-neighbor matching algorithm without replacement,[10] with a caliper width set to 0.2 times the standard deviation of the logit of the propensity score, as this threshold is considered effective in reducing bias without overly restricting the sample size. Following the matching process, diagnostic checks were conducted to assess the adequacy of balance across matched covariates. Standardized mean differences (SMDs) were calculated before and after matching to ensure that residual imbalances were minimized, with an SMD of <0.1 indicating acceptable balance.[11]

Survival analysis

Survival analyses were carried out to evaluate and compare time-to-event outcomes between the early and nonearly G-CSF administration groups. Key outcomes of interest were the time to FN and the time to severe neutropenia. Kaplan–Meier survival curves were constructed to graphically illustrate differences in event-free survival over time between the two groups. The log-rank test was used to assess statistical differences in survival curves.[12]

To further account for potential residual confounding, multivariable Cox proportional hazards regression models were developed to evaluate independent associations between the timing of G-CSF and clinical outcomes. The proportional hazards assumption was assessed using Schoenfeld residuals. The covariates included in the Cox models were age, sex, tumor characteristics, chemotherapy regimens, and baseline hematological parameters. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were reported to quantify the strength and direction of associations.[13]

Sensitivity analyses

Sensitivity analyses were conducted to test the robustness of the results. These included varying the caliper width for PSM,

employing alternative matching methods such as kernel or full matching, and conducting subgroup analyses based on patient subpopulations (e.g. high-risk versus low-risk patients). Missing data were addressed through multiple imputation techniques, ensuring that the analyses remained statistically valid and unbiased.[14] To assess the robustness of our treatment effect estimates, we performed a nearest-neighbor matching analysis. The matching process was designed to ensure an optimal balance between treatment groups while maintaining the largest possible sample size. We also evaluated the consistency of treatment effects across different follow-up periods by applying Cox proportional hazards models to three time windows: 90, 180, and 360 days. We also explored treatment effects across multiple clinical endpoints to validate the comprehensiveness of our findings. Model assumptions were rigorously tested, particularly the proportional hazards assumption for our Cox regression models, using the Schoenfeld residuals test. This comprehensive sensitivity analysis approach aimed to validate the reliability and generalizability of our primary findings.[15]

Statistical software and significance level

All statistical analyses were performed using validated statistical software packages, and a two-tailed $P < 0.05$ was considered statistically significant. The comprehensive application of descriptive statistics, PSM, and survival analysis techniques allowed for a thorough evaluation of the impact of G-CSF administration timing on clinically relevant outcomes in patients undergoing chemotherapy. The analyses were performed using R version 4.2.2 (2022-10-31).[16] Key packages included survival (v3.5.8) for Kaplan–Meier curves and Cox models, survminer (v0.4.9) for survival curve visualization, MatchIt (v4.5.5) for PSM, and tableone (v0.13.2) for baseline characteristic tables and statistical comparisons. Cobalt (v4.5.5) was used for covariate balance diagnostics, whereas dplyr (v1.1.4) and ggplot2 (v3.5.1) were used for data manipulation and visualization. In addition, openxlsx (v4.2.5.2) handled Excel file operations, and svglite (v2.1.1) generated vector graphics.

Results

To achieve group comparability, PSM was performed on 882 patients – 118 in the early treatment group and 764 in the nonearly group. Nearest-neighbor 1:1 matching yielded 118 matched pairs [236 patients; Table 1]. Matching was based on baseline body mass index (BMI), body surface area (BSA), age, and pretreatment laboratory values (ANC, hemoglobin, platelet count). Before matching, substantial imbalances existed (SMD >0.1), notably in hemoglobin (SMD = 0.26) and BSA (SMD = 0.24). After matching, all covariates achieved excellent balance (all SMDs <0.1), with the largest residual imbalance for BMI (SMD = 0.044). This highlights the effectiveness of PSM in reducing baseline differences.

SMDs were used instead of *P* values to assess balance, as *P* values are sample-size dependent and may misrepresent practical differences. In contrast, SMD provides a standardized measure of imbalance magnitude [Figure 1]. All 118 early-treated patients were retained, confirming adequate overlap and ensuring a well-balanced matched cohort for subsequent survival analysis.

In our analysis, the early administration of G-CSF was significantly associated with improved clinical outcomes, including event-free survival, FFS, and NFS. For overall event-free survival, early G-CSF administration was associated with a significantly reduced risk (HR = 0.46; 95% CI: 0.31–0.67; $P < 0.001$), suggesting a strong protective effect compared to nonearly administration. FFS also showed a significant benefit with early G-CSF treatment (HR = 0.36; 95% CI: 0.20–0.67; $P = 0.001$), while NFS was associated with a reduced risk of neutropenia (HR = 0.53; 95% CI: 0.35–0.81; $P = 0.003$), underscoring the role of early G-CSF in mitigating hematologic toxicity.

Due to the NHI reimbursement regulations, no patient in this cohort received true primary prophylactic G-CSF, and all administrations were secondary/reactive following prior neutropenic events. Among the matched cohort of 236 patients, a total of 35 fever events and 63 neutropenia events were recorded during the follow-up period. For NFS, early treatment remained significantly beneficial when analyzed using categorical comparisons ($P = 0.024$), with patients in the nonearly group having a 1.80-fold higher risk of neutropenia (HR = 1.80; 95% CI: 1.08–3.00) compared to those receiving early G-CSF.

Other covariates, including BMI, age, and pretreatment hematologic parameters, were not consistently associated with

Table 1: Baseline characteristics before and after propensity score matching

Variable	Before matching				After matching			
	Control, *n* (%)	Treatment, *n* (%)	*P*	SMD	Control, *n* (%)	Treatment, *n* (%)	*P*	SMD
n	764	118			118	118		
Age	50.90 (10.21)	52.04 (9.66)	0.254	0.115	51.63 (10.53)	52.04 (9.66)	0.751	0.041
BMI	23.24 (3.56)	23.69 (3.51)	0.202	0.127	23.53 (3.57)	23.69 (3.51)	0.729	0.044
BSA	1.56 (0.11)	1.58 (0.12)	0.010	0.243	1.59 (0.12)	1.58 (0.12)	0.865	0.022
Pretreatment ANC	3811.40 (1470.69)	3604.89 (1159.57)	0.146	0.156	3616.34 (1369.52)	3604.89 (1159.57)	0.943	0.009
Pretreatment HGB	12.53 (1.29)	12.19 (1.27)	0.008	0.262	12.20 (1.36)	12.19 (1.27)	0.972	0.004
Pretreatment PLT	246.09 (62.14)	243.34 (71.83)	0.662	0.041	246.10 (66.89)	243.34 (71.83)	0.751	0.040

SMD: Standardized mean differences, ANC: Absolute neutrophil count, HGB: Hemoglobin, PLT: Platelet, BSA: Body surface area, BMI: Body mass index

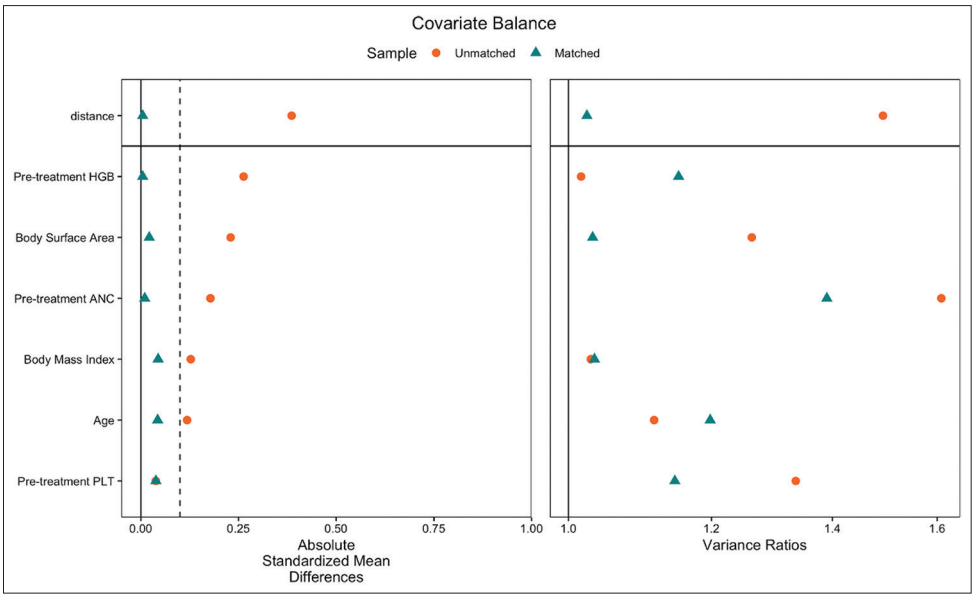

Figure 1: Standardized mean differences (SMDs) before and after matching for key baseline covariates. SMD values are shown for body mass index, body surface area, age, absolute neutrophil count, hemoglobin, and platelet count. Matching substantially reduced imbalance across all variables, with all postmatching SMDs <0.1, indicating successful covariate balance

outcome differences. The only exception was pretreatment ANC, which was significantly associated with NFS ($P = 0.006$), indicating that baseline neutrophil status may influence neutropenia risk regardless of treatment timing.

In total, 78 combined clinical events (including fever, neutropenia, and other events) were documented across both groups. All survival analyses consistently demonstrated statistically significant improvements favoring the early treatment group across all three primary endpoints. These findings further support the efficacy of early G-CSF administration in reducing adverse clinical events and improving patient outcomes. Kaplan–Meier survival curves for NFS [Figure 2], FFS [Figure 3], and overall event-free survival [Figure 4] consistently favored early G-CSF treatment.

Sensitivity analysis results

To assess the robustness of our treatment effect estimates, we performed a nearest-neighbor matching analysis. Before matching, there were notable differences in baseline characteristics between the early and nonearly G-CSF groups, with SMDs ranging from 0.04 to 0.39. After matching, these differences were substantially reduced, with SMDs of 0.005–0.04 across all covariates. The matching process successfully balanced 118 patients in each group (treatment and control), ensuring a more comparable cohort for analyzing treatment effects.

We conducted a sensitivity analysis to evaluate the consistency of treatment effects across different follow-up periods. Cox proportional hazards models were applied to three time windows: 90, 180, and 360 days. While the specific HRs varied slightly between time periods, the overall trend consistently demonstrated a significant protective effect of early G-CSF administration. This temporal consistency suggested that the beneficial impact of early administration was robust and not merely an artifact of a specific time frame.

Our sensitivity analysis explored treatment effects across multiple clinical endpoints. The overall event-free survival showed a significant treatment effect (HR = 0.46; 95% CI: 0.31–0.67; $P < 0.0001$), with similar trends observed in FFS (HR = 0.36; 95% CI: 0.20–0.67; $P = 0.001$) and NFS (HR = 0.53; 95% CI: 0.35–0.81; $P = 0.003$). The consistent direction and statistical significance across these endpoints strengthen the evidence for the protective effect of early G-CSF administration, indicating a comprehensive benefit beyond a single clinical outcome.

We assessed the proportional hazards assumption for our Cox regression models using the Schoenfeld residuals test. For the overall event-free survival, the global test approached but did not quite reach statistical significance ($\chi^2 = 3.53$, $P = 0.06$), suggesting potential minor violations of the proportional hazards assumption. However, the FFS ($\chi^2 = 0.105$, $P = 0.75$) and NFS models ($\chi^2 = 1.59$, $P = 0.21$) demonstrated good adherence to the model's key assumptions. These results enhance the validity of our survival analysis and the reliability of our treatment effect estimates.

Discussion

In this retrospective PSM cohort study, we observed that administering G-CSF 48–72 h after chemotherapy (vs. >72 h) was associated with lower risks of FN, neutropenia, and composite adverse events among patients with early-stage breast cancer receiving adjuvant therapy. Importantly, under the Taiwan NHI policy, all G-CSF administrations in this cohort were secondary prophylaxis/reactive use rather than primary prophylaxis; hence, our comparisons evaluate

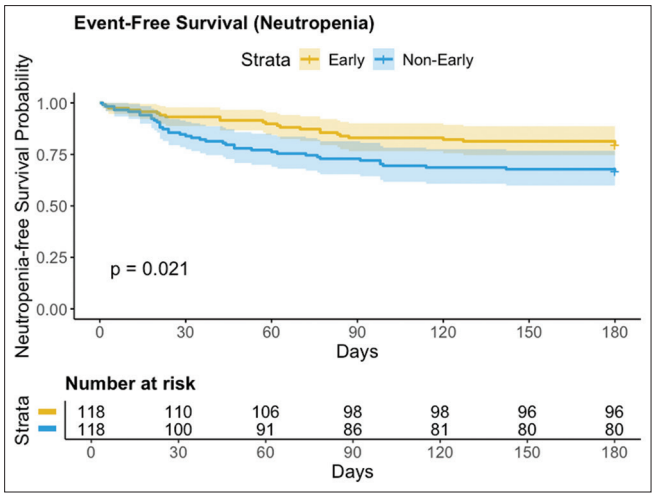

Figure 2: Kaplan–Meier curve for neutropenia-free survival stratified by early versus nonearly granulocyte-colony stimulating factor administration. Early treatment significantly reduced the risk of neutropenia (hazard ratio = 0.53; 95% confidence interval: 0.35–0.81; $P = 0.003$), with 63 neutropenia events documented

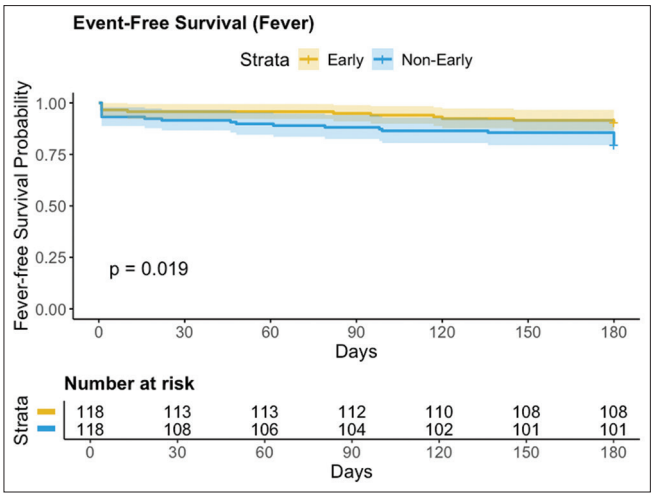

Figure 3: Kaplan–Meier curve for fever-free survival (FFS) stratified by early versus nonearly granulocyte-colony stimulating factor (G-CSF) administration. Early G-CSF treatment was associated with a significantly improved FFS (hazard ratio = 0.36; 95% confidence interval: 0.20–0.67; $P = 0.001$)

timing within a reactive framework, not prophylaxis versus treatment.

PSM substantially improved covariate balance between groups (all postmatch SMDs <0.044), supporting a more comparable assessment of timing effects. In the matched sample, early timing was associated with a 54% lower hazard of any adverse event (HR = 0.46; 95% CI: 0.31–0.67; $P < 0.001$), a 64% lower hazard of fever (HR = 0.36; 95% CI: 0.20–0.67; $P = 0.001$), and a 47% lower hazard of neutropenia (HR = 0.53; 95% CI: 0.35–0.81; $P = 0.003$). These associations remained consistent across multiple sensitivity analyses and follow-up windows.

Our findings are compatible with previous studies suggesting that G-CSF given during early marrow regeneration may support neutrophil recovery. While prior literature has examined windows such as "within 24 h," our definition of early as 48–72 h reflects local clinical workflows and context of the NHI program. Within this reactive setting, earlier administration (48–72 h) compared with nonearly administration (>72 h) showed favorable associations, adding pragmatic guidance where findings in the literature have been inconsistent. Beyond timing, most baseline clinical variables (e.g., age, BMI, hematologic parameters) were not consistently associated with outcomes in adjusted models. A notable exception was pretreatment ANC, which was associated with NFS ($P = 0.006$), suggesting that baseline hematopoietic reserve may modify risk irrespective of timing. Associations were directionally similar across prespecified follow-up windows (90, 180, 360 days), indicating that the observed timing effect was not confined to a single timepoint.

The strengths of this study include (i) rigorous confounding control via PSM with excellent postmatch balance, (ii) prespecified, clinically meaningful endpoints (FFS, NFS, composite events), and (iii) extensive sensitivity analyses (alternative follow-up windows and model checks), which collectively enhanced the internal validity of our results.

The limitations of this study include those inherent to the retrospective, single-center design and to the AC → T regimen focus, which may limit generalizability to other malignancies or regimens. Despite PSM, unmeasured confounding (e.g., clinician judgment, logistics influencing timing within a reactive cycle, adherence, socioeconomic factors) may persist. Heterogeneity in "early" definitions across studies further complicates cross-study comparisons. Clinically, in health care systems where G-CSF is largely reactive/secondary (as in Taiwan), standardizing administration to 48–72 h after chemotherapy may help reduce adverse events and support dose intensity. Implementation outside this context – particularly where primary prophylaxis is routine – should be done with caution and, ideally, prospectively evaluated.

The underlying pathophysiological mechanisms likely explaining our observed benefits of early G-CSF administration deserve further consideration. Chemotherapy-induced neutropenia typically follows a predictable time course, with initial bone marrow suppression followed by a nadir period and eventual recovery. The timing of G-CSF administration appears to be critical in this sequence of events. When administered at 48–72 h postchemotherapy, G-CSF likely coincides with the early phase of myelosuppression, enhancing the proliferation and differentiation of neutrophil precursors before the nadir reaches critical levels.[17]

At the molecular level, G-CSF acts through complex signaling pathways that regulate hematopoietic stem cell mobilization and neutrophil development. G-CSF binds to its

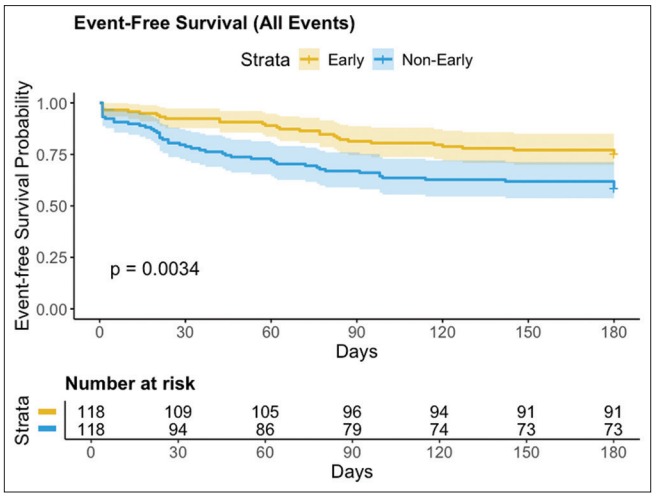

Figure 4: Kaplan–Meier curve for overall event-free survival stratified by early versus nonearly granulocyte-colony stimulating factor (G-CSF) administration. Patients receiving early G-CSF demonstrated better event-free survival (hazard ratio = 0.46; 95% confidence interval: 0.31–0.67; $P < 0.001$), with 78 total events observed during follow-up

receptor (G-CSFR) on hematopoietic stem cells, activating Janus Kinases (JAK)/Signal Transducers and Activators of Transcription (STAT) signaling cascades that upregulate transcription factors essential for granulopoiesis.[17] This leads to increased proliferation of myeloid progenitors, accelerated neutrophil maturation, and enhanced release of mature neutrophils from the bone marrow.[18] The timing of this stimulation relative to chemotherapy-induced damage appears to be crucial, as demonstrated by our findings.

Furthermore, the window of 48–72 h postchemotherapy may represent an optimal balance between allowing sufficient clearance of cytotoxic agents (which could otherwise damage the very progenitor cells that G-CSF aims to stimulate) and intervening early enough to prevent severe neutropenia. Research indicates that immature progenitor cells may not reappear in the bone marrow until approximately 48 h after the administration of chemotherapy, suggesting that this timeframe may align with the optimal cellular environment for the action of G-CSF.[19] The pharmacokinetics of specific chemotherapy agents – doxorubicin, cyclophosphamide, and docetaxel in our study – likely influence this optimal window. These agents have varying half-lives and different mechanisms of myelosuppression, potentially explaining why the 48–72 h window proved effective in our specific chemotherapy regimen.

In addition, G-CSF not only increases neutrophil production but also enhances neutrophil function. While some studies have suggested that G-CSF may temporarily impair neutrophil chemotaxis during stem cell mobilization,[20] others have demonstrated that G-CSF enhances antibody-dependent cellular cytotoxicity, adherence, phagocytosis, and microbial killing.[21] Early administration may, therefore, provide dual benefits of accelerating neutrophil recovery while potentially enhancing the functional capacity of remaining neutrophils during the vulnerable period before complete recovery.

Mathematical modeling of neutrophil dynamics after chemotherapy and G-CSF administration has demonstrated that pharmacokinetics plays a significant role in shaping neutrophil responses.[22] These models suggest that the timing of G-CSF administration relative to the chemotherapy-induced nadir is critical for optimizing neutrophil recovery, providing theoretical support for our clinical findings.

The observed relationship between pretreatment ANC and neutropenia outcomes suggests that baseline hematopoietic reserve influences the response to G-CSF. Patients with a lower baseline neutrophil count may have reduced bone marrow reserve, potentially limiting their response to G-CSF stimulation regardless of timing. This underscores the importance of considering individualized approaches to G-CSF administration that account for baseline hematological parameters.

Future research should focus on prospective validation of these findings in larger, more diverse patient populations and across different chemotherapy regimens. Mechanistic studies examining bone marrow aspirates at various time points after chemotherapy and G-CSF administration could provide direct evidence of the cellular responses underlying our observed clinical benefits.[23] In addition, studies exploring the pharmacokinetic and pharmacodynamic properties of G-CSF administration at different time points, potentially using biomarkers of neutrophil production such as plasma myeloperoxidase or elastase levels, could provide further insights supporting the observed clinical benefits of early administration.[24]

Conclusion

In a reactive/secondary prophylaxis setting under the Taiwan NHI program, earlier G-CSF administration (48-72 h vs. >72 h) was associated with fewer adverse events during adjuvant AC followed by T chemotherapy for early-stage breast cancer. While biologically plausible, these findings reflect observational associations and should be confirmed prospectively, particularly in healthcare systems where primary prophylaxis is common or different regimens are used.

Acknowledgments

We sincerely thank the patients and medical staff at Koo Foundation Sun Yat-Sen Cancer Center for their contributions to this study.

Author contributions

Hsieh-Ting Lin conceptualized and designed the study, performed literature search, collected and analyzed data, conducted statistical analysis, and drafted the manuscript. Lun-Wei Chiou contributed to the study concept and intellectual

content, and assisted in manuscript preparation and editing. Nei-Min Chu contributed to the study concept and clinical studies. Chi-Feng Chung and Peng-Yu Chen contributed to the study concept, clinical studies, and manuscript editing. Chu-Yun Chen and Hsiao-Hsiang Cheng contributed to the study concept and clinical studies. All authors reviewed and approved the final version of the manuscript.

Data availability statement

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cao M, Han S, Qiu Y, Zhou L, Su Y, Tu S, *et al.* Early granulocyte colony stimulating factor administration increases the risk of cytokine release syndrome in acute lymphoblastic leukemia patients receiving anti-CD19 chimeric antigen receptor T-cell therapy. Hematol Oncol 2023;41:933-41.
2. Link H. Current state and future opportunities in granulocyte colony-stimulating factor (G-CSF). Support Care Cancer 2022;30:7067-77.
3. Mahdizadeh M, Karimi MA, Tajabadi Z, Kaveh V, Zamani S. The impact of delayed versus early administration of granulocyte colony-stimulating factor following autologous hematopoietic stem cell transplantation on transplantation outcome. Front Oncol 2024;14:1468948.
4. Liévin R, Di Blasi R, Morin F, Galli E, Allain V, De Jorna R, *et al.* Effect of early granulocyte-colony-stimulating factor administration in the prevention of febrile neutropenia and impact on toxicity and efficacy of anti-CD19 CAR-T in patients with relapsed/refractory B-cell lymphoma. Bone Marrow Transplant 2022;57:431-9.
5. Hsu SW, Chiang SC, Hsu JC, Ko Y. Prescription patterns of granulocyte colony-stimulating factors in patients with breast cancer: A real-world study. PLoS One 2023;18:e0288642.
6. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, *et al.* Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24:5381-7.
7. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika 1965;52:591-611.
8. Upton GJ. Fisher's exact test. J R Stat Soc Ser A Stat Soc 1992;155:395-402.
9. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
10. Thoemmes FJ, Kim ES. A systematic review of propensity score methods in the social sciences. Multivariate Behav Res 2011;46:90-118.
11. Variances Assumed Unequal: cohen's d (av). Available from: https://cran.r-project.org/web/packages/TOSTER/vignettes/SMD_calcs.html. [Last accessed on 2025 Mar 29].
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
13. Farewell VT. An application of cox's proportional hazard model to multiple infection data. J R Stat Soc Ser C Appl Stat 1979;28:136-43.
14. Leamer EE. Sensitivity analyses would help. Am Econ Rev 1985;75:308-13. [Last accessed on 2025 Mar 29].
15. Park S, Hendry DJ. Reassessing schoenfeld residual tests of proportional hazards in political science event history analyses. Am J Polit Sci 2015;59:1072-87. Available from: https://www.jstor.org/stable/24582966. [Last accessed on 2025 Mar 29].
16. R the R Project for Statistical Computing. Available from: https://www.r-project.org/. [Last accessed on 2025 Mar 29].
17. Liongue C, Wright C, Russell AP, Ward AC. Granulocyte colony-stimulating factor receptor: Stimulating granulopoiesis and much more. Int J Biochem Cell Biol 2009;41:2372-75.
18. Winkler IG, Lévesque JP. Mechanisms of hematopoietic stem cell mobilization: When innate immunity assails the cells that make blood and bone. Exp Hematol 2006;34:996-1009.
19. González-Sales M, Craig M, Li J, Nekka F. Efficacy of delayed administration of post-chemotherapy granulocyte colony-stimulating factor: Evidence from murine studies of bone marrow cell kinetics. Exp Hematol 2007;35:1494-501.
20. Thunström Salzer A, Niemiec MJ, Hosseinzadeh A, Stylianou M, Åström F, Röhm M, *et al*. Assessment of neutrophil chemotaxis upon G-CSF treatment of healthy stem cell donors and in allogeneic transplant recipients. Front Immunol 2018;9:1968.
21. Cortjens B, de Boer OJ, de Jong R, Antonis AF, Sabogal Piñeros YS, Lutter R, *et al*. Neutrophil extracellular traps cause airway obstruction during respiratory syncytial virus disease. J Pathol 2016;238:401-11.
22. Brooks G, Provencher G, Lei J, Mackey MC. Neutrophil dynamics after chemotherapy and G-CSF: The role of pharmacokinetics in shaping the response. J Theor Biol 2012;315:97-109.
23. Basu S, Hodgson G, Katz M, Dunn AR. Evaluation of role of G-CSF in the production, survival, and release of neutrophils from bone marrow into circulation. Blood 2002;100:854-61.
24. Papayannopoulos V, Metzler KD, Hakkim A, Zychlinsky A. Neutrophil elastase and myeloperoxidase regulate the formation of neutrophil extracellular traps. J Cell Biol 2010;191:677-91.