SUPPLEMENTARY MATERIALS

Cancer Activity and Clinical Outcomes After Percutaneous Coronary Intervention: A Systematic Review of Bleeding, Ischemic Events, and Evidence Gaps

PROSPERO registration: CRD420261350515

Supplementary Contents

Supplementary Methods S1: Review question, eligibility criteria, and NOS-tool protocol amendment

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Supplementary Results S2: Study-specific cancer activity, clinical outcomes, and antiplatelet reporting

Supplementary Reporting S1–S2: Updated PRISMA checklist; exploratory bleeding certainty/data profiles

Additional verified primary references (from original journal pages): Kwok CS et al. Eur Heart J. 2021;42:1019–1034. doi:10.1093/eurheartj/ehaa1032. Guo W et al. JACC Cardiovasc Interv. 2021;14:1094–1105. doi:10.1016/j.jcin.2021.03.049. Gitto M et al. Eur J Prev Cardiol. 2026;33:537–545 (online 2024). doi:10.1093/eurjpc/zwae399. Ohiomoba R et al. Eur Heart J Open. 2026;6:oeaf163 (online 2025). doi:10.1093/ehjopen/oeaf163.

Supplementary References: Included/excluded studies and reporting-guideline references

Supplementary Methods S1. Review question, protocol, and eligibility

The PROSPERO review was designed to assess outcomes stratified by cancer activity after PCI. The original study-identification evidence is preserved separately from a subsequent targeted literature audit. For a study to be eligible under the operational rule, it must provide a within-cancer activity-specific result, active/historical disease strata, or a within-cancer activity predictor; a no-cancer comparator alone is insufficient.

Table S1. PICOS framework and operational eligibility criteria.

Domain	Prespecified/operational definition	Eligibility rule used in this review
Population	Adults with malignancy undergoing percutaneous coronary intervention (PCI).	Eligible studies had to include a cancer population undergoing PCI and report clinically relevant post-PCI outcomes.
Exposure / index status	Active/current cancer (including ongoing therapy, metastatic/unresectable disease, or current/recent cancer as defined by each study).	Cancer activity definitions were accepted as reported by each original study and were extracted explicitly.
Comparator	History/prior/non-active cancer. Some eligible studies also included a no-cancer comparator.	Activity-stratified outcomes must be separately extractable; no-cancer comparisons alone are ineligible. Within-cancer exploratory contrasts, if outcome-level data are extractable, are eligible.
Antiplatelet context	Post-PCI antiplatelet treatment, principally dual antiplatelet therapy (DAPT).	DAPT use is a clinical context, not an exposure-comparison requirement. No causal or comparative DAPT inference is permitted.
Primary outcomes	Bleeding events and thrombotic complications, including stent thrombosis when reported.	Accepted according to original-study definitions (e.g., BARC bleeding where specified).
Secondary outcomes	Major adverse cardiovascular events (MACE), mortality, recurrent myocardial infarction, stroke, target-lesion revascularization (TLR), and other clinically relevant post-PCI events.	Outcome definitions and follow-up intervals were retained as reported by each study.
Study designs	Comparative clinical studies; the evidence base was expected to be primarily observational.	Randomized and non-randomized comparative studies were eligible; the final included evidence consisted of observational cohorts/registries.
Publication period	2010 to 3 May 2026.	Publication date restriction applied because contemporary DES and antiplatelet practice were the intended context.
Language	English.	Non-English-language reports were excluded.
Exclusions	Non-human studies; studies without PCI/DAPT relevance; studies without eligible clinical outcomes; studies addressing cancer as a new endpoint after DAPT; cancer subgroup reports without extractable cancer-status outcomes; non-eligible disease-specific settings.	Applied during title/abstract screening and full-text assessment as detailed in Tables S5–S6.

Supplementary Methods S2. Information sources and search strategy

The ORIGINAL documented search used MEDLINE (via PubMed), Scopus and Google Scholar (36, 48 and 9 records; 93 in total) through 3 May 2026.

Search reproducibility. Table S2 retains the author-documented original queries. The following broader two-concept searches are proposed for re-execution, using subject headings where supported and removing the mandatory active/history and DAPT terms. PubMed: ("Percutaneous Coronary Intervention"[MeSH] OR "Angioplasty, Balloon, Coronary"[MeSH] OR "percutaneous coronary intervention"[tiab] OR PCI[tiab] OR "coronary stent*"[tiab]) AND ("Neoplasms"[MeSH] OR cancer*[tiab] OR malignan*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR oncolog*[tiab]); date 2010 onward. Scopus: TITLE-ABS-KEY(("percutaneous coronary intervention" OR "coronary stent*" OR PCI) AND (cancer* OR malignan* OR neoplasm* OR tumor* OR tumour* OR oncolog*)). Embase (Emtree and title/abstract terms): ('percutaneous coronary intervention'/exp OR 'coronary stent'/exp OR PCI:ti,ab) AND ('neoplasm'/exp OR cancer*:ti,ab OR malignan*:ti,ab). Google Scholar: screen and log the first 200 ranked results per prespecified complementary query ("PCI cancer active prior outcomes", "PCI malignancy history bleeding", and "coronary stent oncology antiplatelet outcomes"), capturing URLs, date, and duplicates.

Table S2. Database-specific search strategy, limits, date, and yield.

Database / platform	Coverage / date limit	Search date	Search strategy as reported	Records identified	Notes
MEDLINE (PubMed)	2010 to 3 May 2026	3 May 2026	("percutaneous coronary intervention" OR "PCI") AND ("neoplasms" OR "cancer" OR "malignancy") AND ("dual antiplatelet therapy" OR "DAPT" OR "aspirin" OR "clopidogrel" OR "ticagrelor" OR "prasugrel") AND ("active cancer" OR "history of cancer")	36	ORIGINAL strategy only; not the proposed expansion. Exact active/history phrase restriction.
Scopus	2010 to 3 May 2026	3 May 2026	TITLE-ABS-KEY (("percutaneous coronary intervention" OR "PCI") AND ("neoplasms" OR "cancer" OR "malignancy") AND ("dual antiplatelet therapy" OR "DAPT" OR "aspirin" OR "clopidogrel" OR "ticagrelor" OR "prasugrel") AND ("active cancer" OR "history of cancer"))	48	ORIGINAL strategy only; not the proposed expansion. Exact active/history phrase restriction.
Google Scholar	2010 to 3 May 2026	3 May 2026	("percutaneous coronary intervention" OR PCI) AND (neoplasms OR cancer OR malignancy) AND ("dual antiplatelet therapy" OR DAPT) AND ("active cancer" OR "history of cancer")	9	ORIGINAL strategy only; not the proposed expansion. Google Scholar screening depth undocumented.

Table S3. Search-reporting details aligned with PRISMA-S principles.

Reporting element	Review-specific information	Status / note
Information sources	Original: MEDLINE, Scopus, Google Scholar. Expanded search: Embase and citation chaining proposed, not executed.	Reported
Database platform	PubMed explicitly reported for MEDLINE; Scopus and Google Scholar named	Reported
Date of last search	3 May 2026	Reported
Date limits	Publications from 2010 onward	Reported
Complete Boolean concepts	PCI; malignancy; DAPT/antiplatelets; cancer activity/history	Reported in Table S2

Reporting element	Review-specific information	Status / note
Language restriction	English-language studies eligible	Applied at selection stage
Record management / deduplication	Zotero; 19 duplicates removed	Reported
Search peer review	No PRESS or equivalent search peer-review process documented in the supplied files	Not documented
Citation searching / hand-searching	Not documented in original; backward/forward checking required on rerun.	Not documented
Search update	Final search date explicitly stated; no later update documented	Expanded rerun is still required; do not change PRISMA counts.
Search-history export	Native database history/export not present in supplied files	Original platform exports unavailable; retain retrieval logs for new searches.

Supplementary Methods S3. Study selection, data extraction, and synthesis

The original methods report independent duplicate title/abstract and full-text screening of the 93-record search. Independently duplicated extraction, NOS/GRADE judgments, and updated independent screening have not been documented.

Table S4. Data-extraction framework used for the qualitative synthesis.

Data domain	Variables extracted	How handled in synthesis	Reason for inclusion
Bibliographic / design	First author; publication year; design; setting; sample size	Tabulated by study	Characterizes evidence base and design heterogeneity
Cancer status	Active/current; non-active/prior/history; ongoing cancer treatment; study-specific definitions	Retained verbatim or summarized without imposing a uniform definition	Central exposure/comparator of the review
PCI context	AMI/ACS vs broader PCI; first PCI; primary PCI; registry/administrative cohort	Tabulated	Important source of baseline risk heterogeneity
Antiplatelet exposure	DAPT use; antiplatelet context; treatment modification/duration when available	Narratively summarized; missing regimen details explicitly acknowledged	Core clinical context of the review
Follow-up	In-hospital, 1 year, median/mean long-term follow-up	No forced harmonization across studies	Outcome risk is time-dependent
Bleeding	BARC bleeding, major bleeding, other study-defined bleeding	Reported using original definitions	Primary safety domain
Thrombotic / ischemic events	Stent thrombosis when available; recurrent MI; stroke; TLR; study-defined MACE	Reported using original definitions	Primary/secondary efficacy domain
Mortality	All-cause, cardiovascular, non-cardiac, in-hospital or follow-up mortality	Reported by time horizon	Important competing-risk/prognostic outcome in cancer populations
Effect estimates	Adjusted HR/OR/RR and 95% CI when reported; otherwise event rates and p values	No pooled effect estimate generated	Avoids combining non-comparable metrics
Study limitations	Residual confounding; incomplete cancer-treatment data; administrative coding; short follow-up	Integrated into narrative interpretation	Supports cautious causal interpretation

Supplementary Methods S4. Risk-of-bias assessment

The original five reports were appraised using the Newcastle–Ottawa Scale (NOS); selected items were reassessed conservatively. Numerical star cutoffs are not validated categories of bias severity.

Table S7. Newcastle–Ottawa Scale domains and decision rules applied in this review.

Domain	NOS item	Maximum stars	Operational interpretation
Selection	Representativeness of exposed cohort	1	Cohort reasonably representative of the relevant PCI population.
Selection	Selection of the non-exposed/comparator cohort	1	Comparator drawn from the same or a comparable source population.
Selection	Ascertainment of exposure	1	Cancer status/exposure ascertained from clinical/registry records or a similarly robust source.
Selection	Outcome not present at start	1	The assessed outcome was absent at baseline or the temporal sequence was clear.
Comparability	Control for confounding	2	Up to two stars for appropriate adjustment/comparability on important clinical covariates.
Outcome	Assessment of outcome	1	Outcome obtained from record linkage, clinical follow-up, adjudication, or equivalent.
Outcome	Follow-up long enough	1	Follow-up judged sufficient for the outcome being evaluated.
Outcome	Adequacy of follow-up	1	Follow-up completeness judged adequate or loss to follow-up unlikely to bias results.

Table S8. Newcastle–Ottawa Scale risk-of-bias assessment of included studies.

Study	Represent.	Comparator cohort	Exposure	Outcome absent	Comparability	Outcome assess.	Follow-up long enough	Follow-up adequacy	Total / 9	Overall
Nishikawa et al. (2021)	–	★	★	★	★	★	★	★	7	Not assigned
Matsumoto et al. (2021)	★	★	★	★	★★	★	★	★	9	Not assigned
Kanenawa et al. (2021)	★	★	★	★	★	★	★	★	8	Not assigned
Tabata et al. (2018)	★	★	★	★	★★	★	★	★	9	Not assigned
Potts et al. (2019)	★	★	★	★	–	★	–	★	6	Not assigned
Kwok et al. (2021)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Guo et al. (2021)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Gitto et al. (2024/2026)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

Study	Represent.	Comparator cohort	Exposure	Outcome absent	Comparability	Outcome assess.	Follow-up long enough	Follow-up adequacy	Total / 9	Overall
Ohiomoba et al. (2025/2026)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

Potts contributes only index-hospitalization outcomes. Kwok contributes 90-day readmission outcomes using a separate national claims source but potentially overlapping time periods. Ohiomoba provides long follow-up and DAPT refill-gap exposure, but its treatment contrasts are observational.

Supplementary Results S1. Study selection

Table S5. Study-selection accounting corresponding to the PRISMA flow diagram.

Stage	Number	Reason / category	Accounting
Records identified	93	PubMed 36; Scopus 48; Google Scholar 9	36 + 48 + 9 = 93
Duplicates removed	19	Duplicate records	93 − 19 = 74
Titles/abstracts screened	74	All unique records	74
Excluded at title/abstract stage	60	No cancer n=24; no PCI/DAPT n=24; no relevant PCI outcomes n=6; cancer as endpoint n=4; cancer subgroup without specific outcomes n=2	24 + 24 + 6 + 4 + 2 = 60
Full-text reports assessed	14	Potentially eligible after title/abstract screening	74 − 60 = 14
Full-text reports excluded	9	Cancer vs non-cancer only/non-eligible comparison n=5; specific gastric cancer/endoscopic setting n=2; cancer-related death after extended DAPT n=1; cancer HBR score n=1	5 + 2 + 1 + 1 = 9
Studies included	5	Final qualitative synthesis	ORIGINAL: 14 − 9 = 5; targeted verification identified five more potentially eligible reports

Table S6. Reports excluded after full-text assessment and primary reason for exclusion.

Report	Year	Primary reason for exclusion	Review-specific rationale
Campos et al. Risk Burden of Cancer in Patients Treated With Abbreviated DAPT After PCI	2024	Cancer versus non-cancer comparison without the required active/prior cancer comparison	Excluded under the same rule for every report: no extractable active/current versus prior/non-active cancer clinical outcome contrast; cancer versus no-cancer or DAPT-duration comparisons alone are insufficient. Confirm after expanded rescreen.
Cordova Sanchez et al. Acute Myocardial Infarction in Patients with Cancer: Outcomes and P2Y12 Inhibition	2025	Cancer versus non-cancer comparison / non-eligible cancer-status contrast	Excluded under the same rule for every report: no extractable active/current versus prior/non-active cancer clinical outcome contrast; cancer versus no-cancer or DAPT-duration comparisons alone are insufficient. Confirm after expanded rescreen.
Aziz et al. Coronary Stent Healing in Cancer Patients—An OCT Perspective	2021	Non-eligible cancer-status comparison and mechanistic imaging focus	Focused on stent healing/OCT rather than the prespecified comparative clinical outcome framework.

Report	Year	Primary reason for exclusion	Review-specific rationale
Ohiomoba et al. Relationship of Cancer and DAPT Duration to Long-Term Ischaemic and Bleeding Outcomes after PCI	2026	Incorrectly excluded in original review: active vs inactive cancer outcomes are reported in full 2025/26 article.	This article meets the operational cancer-activity rule and must be retained for independent updated screening; the 2026 meeting abstract duplicates the earlier full paper.
Santoro et al. Single, Dual, and Triple Antithrombotic Therapy in Cancer Patients with CAD	2021	Non-primary review article / no eligible comparative cohort	Secondary evidence synthesis rather than an eligible original comparative study.
Sato et al. Postoperative Bleeding after Gastric Endoscopic Submucosal Dissection	2017	Specific gastric/endoscopic population; not PCI	Bleeding after gastric endoscopic submucosal dissection, outside the PCI review setting.
Harada et al. Gastric Endoscopic Submucosal Dissection with Continuous Low-Dose Aspirin	2019	Specific gastric/endoscopic population; not PCI	Endoscopic bleeding study rather than post-PCI DAPT outcomes.
Mauri et al. Causes of Late Mortality with Dual Antiplatelet Therapy after Coronary Stents	2015	Cancer/cancer-related mortality as an outcome rather than cancer as baseline exposure	Did not address post-PCI outcomes stratified by active versus previous cancer.
Dafaalla et al. Updated PRECISE-DAPT Cancer Score	2024	Risk-score development/validation	Objective was bleeding-risk prediction rather than comparative active-versus-history cancer outcomes.

Supplementary Results S2. Included studies and extracted outcomes

Table S9. Characteristics of the five originally included and five additionally identified potentially eligible studies

Study	Design / setting	Population	Cancer-status groups	PCI context	Follow-up	Main outcome domain	Key finding relevant to review
Nishikawa et al. (2021)	Observational cohort; Osaka International Cancer Institute, Japan	89 patients with solid cancer undergoing first PCI	Active: inoperable treatment/metastasis n=45; non-active: resection done/planned n=44	ACS n=12/89; otherwise non-ACS; median DAPT 8 vs 10 months	Median 2.2 years	BARC 2,3,5 bleeding (10/45 vs 1/44); 3P-MACE	Bleeding was significantly more frequent in active cancer (p=0.010); cancer activity independently predicted bleeding, without a significant increase in 3-point MACE.
Matsumoto et al. (2021)	Bi-center registry; Japan	903 patients with acute MI undergoing primary PCI	Active cancer n=49; history of cancer n=65; no cancer n=789	Primary PCI for AMI	Mean 853 days after discharge plus in-hospital outcomes	Study-defined major bleeding: in-hospital 10/49 vs 4/65 vs 46/789; full-text BARC definition unverified	In-hospital major bleeding: 20.4% vs 6.2% vs 5.8% (p=0.002); active cancer also had higher post-discharge MACE and major bleeding.
Kanenawa et al. (2021)	Retrospective/observational cohort; Kokura Memorial Hospital, Japan	1,303 consecutive first-PCI patients; 185 had present/history of cancer	Ongoing therapy n=18 vs recent (<12 months), no ongoing therapy n=59; remote prior n=108	First PCI; ACS 494/1,303; DAPT common but regimen not compared	1 year	BARC 3/5 bleeding (3/18 vs 2/59); NACCE; non-cardiac mortality	Cancer was associated with higher non-cardiac death (4.4% vs 1.5%, p=0.006). Ongoing cancer therapy was associated with higher major bleeding than recent cancer without ongoing therapy (16.7% vs 3.4%, p=0.049).
Tabata et al. (2018), KUMA	Single-center observational cohort; Kumamoto University, Japan	701 PCI patients	Main adjusted estimate: any vs no cancer. Time since treatment is an exploratory subgroup finding (within cancer).	PCI	1 year	Target-lesion revascularization (TLR)	Malignancy predicted TLR (HR 2.28, 95% CI 1.30–4.00; p=0.004); current/recent cancer history carried the greatest recurrent-event burden.
Potts et al. (2019)	Nationwide retrospective administrative cohort; U.S. Nationwide Inpatient Sample	6,571,034 PCI procedures (2004–2014)	Current cancer 1.8%; previous cancer 5.8%; no cancer	All PCI in administrative dataset	In-hospital	Mortality and in-hospital complications, including bleeding	In-hospital prognostic context only, not post-discharge DAPT evidence; administrative codes cannot adjust for stage or regimen.

Study	Design / setting	Population	Cancer-status groups	PCI context	Follow-up	Main outcome domain	Key finding relevant to review
Kwok 2021	Nationwide Readmissions Database	1,933,324 US PCI records	Active 2.7%; historical 6.8%; none remainder	Mixed ACS/CCS	90 days	AMI/bleeding readmissions	Rates according to cancer status and tumor type; additional current vs prior detail requires full-text review.
Guo 2021	Mayo Clinic PCI; propensity matched	416 cancer + 768 no cancer	Active defined by active treatment at PCI; cancer survivor subgroup	Mixed PCI	5 years	BARC 2+ bleeding; MI; ST	Active cancer independently predicts bleeding within cancer; main group estimates vs noncancer.
Gitto 2024 online / 2026 issue	Mount Sinai CathPCI registry	2,007 cancer patients	307 active (diagnosed <12 months or undergoing therapy); 1,700 remission	Mixed	1 year	Registry-defined major bleed; MACCE	Status-stratified event counts recoverable from HBR strata; KM percentages differ from crude fractions.
Ohiomoba 2025 online / 2026 issue	National VA administrative/clinical cohort	40,677 PCI patients	791 active chemo/radiotherapy; 7,633 inactive; 32,253 without cancer	Mixed	Mean 5.4 years	ICD-coded major bleed; MI; death; DAPT discontinuation	Long-term cancer activity and DAPT fill-gap analysis; adjusted HRs use no-cancer reference.
Ueki 2019	Prospective Bern PCI registry	13,647 PCI; cancer n=1,368	Recent diagnosis ≤1 y n=203; ongoing therapy n=179; older diagnosis remainder	ACS/CCS; discharge DAPT and potent P2Y12 reported, not status-stratified	1 year	BARC 2–5 bleeding; cardiac death; DOCE	Recent cancer diagnosis independently predicted BARC 2–5 bleeding; no verified event counts for active-vs-prior RR.

Table S10. Outcome-level interpretation and sources of heterogeneity.

Outcome / construct	Studies contributing	How defined/reported	Direction of evidence	Why not quantitatively pooled
Bleeding	Nishikawa; Matsumoto; Kanenawa; Ueki; Gitto; Ohiomoba; Potts (in-hospital context); Guo (activity predictor); Kwok (90-day readmissions)	BARC 2–5, BARC 3/5, study-/registry-/ICD-coded bleeding; follow-up from index hospitalization to years. Five recoverable within-cancer event-count contrasts.	Direction generally favors greater bleeding with active or recently diagnosed cancer, although inactive cancer is not risk-free.	Contrasts, time horizons, treatment groups, ascertainment and adjustment differ; no pooled estimand.
MACE, MI, stent thrombosis, revascularization	Nishikawa; Matsumoto; Tabata; Ueki; Guo; Kwok; Ohiomoba	MACE composites, MI, stent thrombosis, TLR, readmissions; some outcomes presented only versus no cancer.	Ischemic results less consistent than bleeding; active-versus-prior adjusted causal contrast not available.	Composite constituents and comparator definitions non-comparable; competing death varies.
Mortality	Matsumoto; Kanenawa; Tabata; Potts; Ueki; Guo; Ohiomoba; Kwok	In-hospital, one-year and longer-term all-cause/cardiac/non-cardiac death.	Active cancer generally associated with worse noncardiac and overall prognosis; PCI-related causation not established.	Cancer type/stage and competing mortality vary; overlapping US samples possible.
Cancer activity definitions	All ten source-verified reports	Active/current/recent diagnosis, active treatment, metastasis, remission and administrative code-defined status are operationally distinct.	Precise cancer-activity classification matters; simple cancer-versus-none grouping conceals heterogeneity.	Cannot collapse the states into one universally comparable exposure.
DAPT/P2Y12 exposure	Ohiomoba (longitudinal fill-gap/discontinuation); Ueki, Nishikawa and others (partial); remaining studies incomplete	Variable initial DAPT, potent P2Y12, actual duration, discontinuation windows and antiplatelet interruption.	Observational DAPT-discontinuation associations available, but no cancer-activity randomized strategy contrast.	Confounding by indication and clinical time-varying factors prevent causal regimen recommendations.

Supplementary Reporting S1. PRISMA 2020 checklist

The PRISMA checklist distinguishes the ORIGINAL May 2026 search (93 records; five included) from a targeted October 2026 evidence verification (five additional primary studies).

Table S11. PRISMA 2020 checklist mapped to the manuscript and Supplementary Materials.

PRISMA item	Topic	Concise reporting requirement	Location in current submission
1	Title	Identify the report as a systematic review.	Revised title states “A Systematic Review.”
2	Abstract	Provide a structured summary of objectives, eligibility, information sources, methods, results, limitations, implications, and registration.	Revised abstract, ≤200 words; eligibility, uncertainty and registration specified.
3	Rationale	Describe the rationale in the context of existing knowledge.	Introduction, revised manuscript.
4	Objectives	State the review objective/question explicitly.	Introduction, ; PICOS, ; Table S1.
5	Eligibility criteria	Specify inclusion/exclusion criteria and grouping for synthesis.	Methods, ; Table S1.
6	Information sources	Specify all databases/sources and date each was last searched.	Main Methods 2.2; original source dates/Table S2 and expanded strategy (pending execution).
7	Search strategy	Present full search strategies, filters, and limits.	Original exact strings, Table S2; expanded proposed strings, Supplementary Methods S2 (execution pending).
8	Selection process	Describe how records/reports were screened and how disagreements were resolved.	Methods, revised manuscript.
9	Data collection process	Describe how data were extracted, reviewer roles, and any author contact/automation.	Methods 2.4; independent screening reported; duplicate extraction not verified.
10a	Data items — outcomes	List and define all outcomes sought and rules for selecting results.	Abstract/Methods, revised manuscript and 4; Tables S1 and S4.
10b	Data items — other variables	List other variables sought and assumptions for missing/unclear information.	Methods 2.4 and Table S4; missing values labeled not reported, no imputation.
11	Risk of bias	Specify tool, domains, reviewers, and judgement process.	Methods 2.5, Table S8; duplicate assessment roles not documented, author confirmation pending.
12	Effect measures	Specify effect measures for each outcome.	Study-level HR/OR/event rates reported as available; no common pooled effect measure used. Table S10.
13a	Synthesis eligibility	Describe how studies were assigned to each synthesis.	Tables S1, S4, S9–S10.
13b	Data preparation	Describe transformations or handling of missing summary statistics.	No transformations undertaken; no meta-analysis.
13c	Display methods	Describe methods used to tabulate or visually display results.	Main Table 1, Figure 2 (unpooled); Tables S9–S10 and S13.
13d	Synthesis methods	Describe synthesis methods and rationale.	Supplementary Methods S3; qualitative narrative synthesis.
13e	Heterogeneity exploration	Describe methods used to explore heterogeneity.	No statistical heterogeneity analysis; clinical/methodological heterogeneity summarized in Table S10.
13f	Sensitivity analyses	Describe sensitivity analyses.	Not performed; no quantitative synthesis.

PRISMA item	Topic	Concise reporting requirement	Location in current submission
14	Reporting-bias assessment	Describe methods used to assess bias due to missing results.	Not formally assessed: five heterogeneous studies; asymmetry testing inappropriate.
15	Certainty assessment	Describe methods for certainty/confidence in the body of evidence.	Methods 2.5 and exploratory GRADE bleeding profile, Table S12.
16a	Study selection results	Report records identified, screened, excluded, and included, preferably with flow diagram.	Figure 1 and Table S5 (original documented search only; update after re-execution).
16b	Excluded studies	Cite apparently eligible studies excluded at full text and explain why.	Table S6.
17	Study characteristics	Cite each included study and present key characteristics.	Main Table 1 and Supplementary Table S9 (ten identified reports, five new candidates subject to eligibility adjudication).
18	Risk of bias in studies	Present risk-of-bias assessments for each study.	Methods 2.5; original five NOS items in Table S8; five additional reports not independently appraised (incomplete).
19	Individual-study results	For each study, present outcome data and effect estimates/precision when available.	Main Results 3.4, Figure 2, Table S13; precision of crude ratios indicated.
20a	Synthesis results — contributing studies	Summarize characteristics and risk of bias of studies contributing to each synthesis.	Discussion, ; Tables S8–S10.
20b	Synthesis results — meta-analysis	Report pooled estimates and heterogeneity if meta-analysis was performed.	Not applicable: no meta-analysis performed.
20c	Heterogeneity investigations	Present results of investigations of causes of heterogeneity.	No formal subgroup/meta-regression analyses; qualitative sources listed in Table S10.
20d	Sensitivity analyses	Present sensitivity-analysis results.	Not performed.
21	Reporting biases	Present assessments of bias due to missing results.	Not assessed formally; publication and selective reporting bias cannot be ruled out.
22	Certainty of evidence	Present certainty/confidence for each outcome.	Original exploratory bleeding GRADE only (very low); no completed updated body-of-evidence certainty appraisal.
23a	Discussion — interpretation	Interpret results in context of other evidence.	Discussion, revised manuscript.
23b	Discussion — evidence limitations	Discuss limitations of the included evidence.	Discussion 4.4: methodological, study-level, and certainty limitations.
23c	Discussion — review-process limitations	Discuss limitations of review methods.	Discussion 4.4: restrictive original search, no Embase, GS-depth ambiguity, no citation chaining.
23d	Discussion — implications	Discuss implications for practice, policy, and future research.	Discussion 4.4; Future Directions; Conclusions.
24a	Registration	Provide registry name and registration number.	PROSPERO CRD420261350515; Methods 2.1.
24b	Protocol	Indicate where protocol can be accessed.	PROSPERO registration and Supplementary Methods S1.
24c	Amendments	Describe and explain amendments to registration/protocol.	Supplementary Methods S1 and S4: use of NOS rather than ROBINS-I.

PRISMA item	Topic	Concise reporting requirement	Location in current submission
25	Support	Describe financial/non-financial support and funder role.	Funding statement in Back Matter.
26	Competing interests	Declare competing interests.	Conflicts of Interest statement in Back Matter.
27	Availability of data/code/materials	State availability of extraction forms, extracted data, analysis code, and other materials.	Supplementary Materials include methods, original search accounting, extraction domains, study-level results, risk-of-bias assessment, certainty profile, and exploratory effect estimates; source-level extraction files are not included.

Supplementary Reporting S2. Exploratory bleeding estimates and certainty appraisal

Table S12. Exploratory GRADE-domain certainty assessment for active/current versus less-active cancer and bleeding.

Outcome / comparison	Evidence	Domain judgments	Certainty	Interpretation
Bleeding: active/ongoing treatment vs prior/non-active/recent untreated cancer	Three observational cohorts (Nishikawa, Matsumoto, Kanenawa); heterogeneous follow-up	Risk of bias: serious (confounding, selected samples); inconsistency: direction concordant but definitions differ; indirectness: serious (different activity contrasts/endpoints); imprecision: serious (few events/wide CIs); publication bias unknown	VERY LOW (post hoc exploratory appraisal)	The direction of association is suggestive; confidence in the magnitude is very limited. This profile does not support treatment recommendations.

Table S13. Crude unadjusted bleeding risk ratios used in Figure 2 (no meta-analysis).

Study	Active events/total	Comparator events/total	Bleeding definition	Follow-up	Crude RR (95% CI)
Nishikawa 2021	10/45	1/44	BARC 2/3/5	BARC 2/3/5; median 2.2 y	9.78 (1.31–73.21)
Matsumoto 2021	10/49	4/65	In-hospital major bleeding	In-hospital major bleeding	3.32 (1.11–9.95)
Kanenawa 2021	3/18	2/59	BARC 3/5	BARC 3/5; 1 y	4.92 (0.89–27.17)
Gitto 2024/26	37/307	114/1700	Registry-defined	Registry-defined; 1 y	1.80 (1.27–2.55)
Ohiomoba 2025/26	133/791	1030/7633	ICD-coded major bleeding	ICD-coded major bleeding; mean 5.4 y	1.25 (1.06–1.47)

Exploratory calculation: RR=(a/n1)/(c/n0), log-normal 95% CI=exp[ln(RR) ± 1.96×sqrt(1/a−1/n1+1/c−1/n0)]. No continuity corrections were necessary. Point estimates are not adjusted HRs, cannot be pooled across nonuniform outcomes, and are sensitive to follow-up. The Gitto 37 and 114 counts were summed across mutually exclusive HBR subgroups (active 32+5, remission 87+27); the Ohiomoba 133 and 1030 counts were transcribed directly from its outcomes table. All other input counts were checked against original summaries.

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