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THE PARADOX OF MORPHINE IN CANCER CARE: A META-ANALYSIS OF SURVIVAL, DEATH, AND RECURRENCE OUTCOMES

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ABSTRACT – *Objective:* Morphine is a common opioid used for managing pain in cancer patients, but its effects on survival, death, and cancer recurrence are unclear. While its pain-relieving properties are well-known, concerns about its impact on tumor progression and overall prognosis remain unresolved. This systematic review and meta-analysis aimed to assess the influence of morphine on these critical cancer-related outcomes.

Patients and Methods: A systematic review was conducted following PRISMA guidelines. Databases, including PubMed, Scopus, Web of Science, and Google Scholar, were searched for studies published until August 18, 2024, that evaluated the effects of morphine on survival, death, and recurrence in cancer patients. Data were extracted from 33 studies involving 373,882 cancer patients. Statistical analyses were performed using STATA, including subgroup analyses and meta-regression to assess the impact of morphine dose, route of administration, and follow-up periods on outcomes.

Results: Higher doses of morphine were linked to lower survival rates, with very high doses showing a 13% decrease in survival (95% CI: 3-24%). In contrast, intravenous administration was associated with higher survival rates (47%, 95% CI: 40-54%). High oral doses significantly increased mortality risk (HR = 16.09, 95% CI: 6.29-25.89), while recurrence was most frequent with moderate doses (46%, 95% CI: 38-54%) and intravenous morphine (38%, 95% CI: 33-42%).

Conclusions: Morphine's impact on cancer outcomes varies with dose and route of administration. Higher doses, especially oral, are linked to worse survival and increased mortality. Clinicians should balance morphine's analgesic benefits with these potential risks. Further research is necessary to refine opioid use in cancer care.

KEYWORDS: Morphine, Cancer, Survival, Death, Recurrence.

INTRODUCTION

Morphine is a potent opioid analgesic and has long served as a cornerstone in the management of severe cancer-related pain[1]. Its ability to alleviate pain and improve quality of life in patients with advanced malignancies is well-documented[2]. However, the broader implications of morphine use, particularly its potential impact on cancer-related outcomes such as survival, recurrence, and overall mortality, have become subjects of increasing concern[3-6].

Recent studies have suggested that opioids, including morphine, may exert effects beyond pain relief, potentially influencing tumor biology through various mechanisms[7]. These effects may include modulation of the immune response, alteration of tumor cell proliferation, and impacts on angiogenesis.

While some preclinical studies have indicated that morphine might inhibit tumor growth, others have raised the possibility that it could promote tumor progression or metastasis, particularly at higher doses[8]. This dichotomy underscores the need for a more nuanced understanding of how morphine use in cancer patients might affect clinical outcomes beyond pain management.

The role of morphine in influencing cancer prognosis is further complicated by variations in its administration. Factors such as the dose, route of administration (e.g., oral, intravenous, subcutaneous), and duration of use may all contribute to differing outcomes. Additionally, patient-specific factors (i.e., type and stage of cancer, comorbidities) may interact with these variables, making it challenging to draw definitive conclusions from existing studies[9,10].

Given the widespread use of morphine in cancer care and the potential implications of its impact on survival and recurrence, there is an urgent need for a comprehensive evaluation of the available evidence. While several observational studies have explored the relationship between morphine use and cancer outcomes, the findings have been inconsistent[3,5,11-13]. This is reflected in the heterogeneity in study design, patient populations, and methodologies. To date, no large-scale systematic review and meta-analysis have thoroughly examined the effect of morphine on cancer-related outcomes, particularly route- and dose-specific effects.

This study aims to fill this gap by conducting a systematic review and meta-analysis to assess the impact of morphine on survival, death, and recurrence in cancer patients. By synthesizing data from a broad range of studies, we seek to provide clearer insights into the potential risks and benefits of morphine use in this population.

PATIENTS AND METHODS

Research Design

This systematic review and meta-analysis study included studies that discussed the imposed harm of morphine use in cancer patients in terms of survival, death, or recurrence. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for individual patient data meta-analysis[14]. The review's protocol was not registered prospectively on PROSPERO.

Information Sources

The identification and selection of relevant patient records was done through a systematic literature search of PubMed, Scopus, Web of Science, and Google Scholar. In the latter, only the first 200 records were screened as per recent recommendations[15]. The search included studies that were published from inception (January 1, 1980) until August 18th, 2024. The original search query included the following terms: morphine AND cancer OR carcinoma OR malignancy OR malignant AND survival OR recurrence OR death OR mortality. The detailed search criteria used in identifying relevant cases are provided in Table S1. Our institution's librarian carried out the literature search.

Moreover, a manual search step was done to ensure the inclusion of all eligible studies without missing any potentially relevant studies[16]. This was done by (1) searching similar articles on PubMed using the "similar articles" option, (2) searching the citations of included studies, and (3) searching Google software using the same keywords employed in the original database search.

Record Selection (eligibility criteria)

The eligibility criteria were formatted according to the PICOS framework (Population, Intervention, Comparison, Outcomes, Study Design) as follows:

Inclusion criteria:

- Population: patients with any type or stage of cancer.
- Intervention: morphine of any dose, route, or setting (home-based care, in a hospital setting, or outpatient).
- Comparison: not specified.
- Outcomes: any survival data, death/mortality, or recurrence.
- Study design: any original study design with >5 cases.
- Reports published in any language.

Exclusion criteria:

- Non-original research (review articles, editorials, commentaries)
- Case reports and case series with less than 5 patients
- Studies that described morphine intake in cancer patients without reporting survival data (or death or recurrence)
- Abstract-only publication
- Duplicated records
- Irrelevant outcomes (respiratory depression, pain, stroke, quality-of-life, etc.)

Data Extraction and Methodological Quality Assessment

A standardized data collection form was developed to ensure consistency in extracting relevant information from each report. The form included fields for patient demographics (age, gender), clinical presentation (cancer type, metastasis, patient setting), morphine characteristics (morphine equivalent daily dose (MEDD, mg/day)), and clinical outcomes (survival, death, recurrence). Different survival measures were of interest: overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), and recurrence-free survival (RFS). Morphine administration was categorized into low dose (MEDD <60 mg/day), moderate dose (MEDD 60-299 mg/day), high dose (MEDD 300-599 mg/day), and very high dose (MEDD >600 mg/day) [17]. We used the categorization system instead of dealing with it as a continuous variable because, in most studies, the MEDD data were provided as a range.

Before full-scale data extraction, the form was pilot-tested on a small subset of studies to ensure its reliability and comprehensiveness. Any discrepancies identified during this phase were resolved, and the form was refined accordingly. Two independent reviewers extracted data from each included study. This process involved a thorough review of each report to capture all relevant information. Where necessary, the reviewers contacted the original authors (through emails, ResearchGate, or LinkedIn) for clarification on specific data points.

Discrepancies between the reviewers were resolved through discussion and, if necessary, consultation with a third reviewer. This approach minimized the risk of data extraction errors and ensured the accuracy of the collected data. The methodological quality of the included reports was assessed using the Newcastle Ottawa Scale for Observational studies[18]. Each study is assessed over three domains: selection (4 questions, 4 stars), comparability (1 question, 2 stars), and outcome (3 questions, 3 stars). Finally, each study is given an overall quality of good (3-4 stars in selection plus 1-2 stars in comparability plus 2-3 stars in outcome), fair (2 stars in selection, 1-2 stars in comparability, and 2-3 stars in outcomes), or poor (0-1 star in selection, 0 stars in comparability, and 0-1 star in outcome).

Data Analysis

Statistical analyses used STATA (Version 18, Stata Corp, USA), following a predefined plan without adjustments. We used the pooled effect size [ES] and its corresponding 95% confidence interval (CI) to report the pooled incidence rate for survival, death, and recurrence. Additionally, we pooled the reported hazards ratio (HR) of the adjusted Cox-proportional Hazards model of survival or death across included studies. Given the highly heterogeneous samples pooled at baseline, a pooled meta-analysis was deemed infeasible. Therefore, subgroup analyses were done to account for these factors. We employed a random-effects model and used the last observation carried forward method to handle data heterogeneity and minimize missing data risks[19]. Heterogeneity was quantified using the I^2 statistic, with significant heterogeneity defined as I^2>40%[20]. Sensitivity analyses tested the robustness of results with Galbraith plots identifying outliers, and publication bias was assessed with funnel plots and asymmetry tests (if >10 studies are reported)[21].

Subgroup analyses examined potential effect modifiers, such as assessment period, morphine dosage (low, moderate, high, very high), and route of administration (oral, IV, etc.). Meta-regression assessed the impact of study-level covariates (sample size, mean age, gender (male %), metastasis rate (%), and morphine dose/route of administration). We adjusted for multicollinearity, defined with variance inflation factor – VIF >5[22]. Model fit was assessed with the adjusted R-squared (higher values reflect better fit). Variables reported by at least five studies were eligible for subgroup and meta-regression (significant heterogeneity is mandatory)[23].

RESULTS

Literature Search Results

The results of the literature search and study selection processes are illustrated in Figure 1. In summary, we identified 1930 records from the literature search, of which 837 were ruled out as duplicates through EndNote Software. Following the screening of 1093 titles and abstracts, only 95 articles were sought for full-text retrieval, four of which were inaccessible. The main (first and corresponding) authors of these articles were contacted, but no response was received. Fifty-eight articles were then excluded because they reported pain data without survival outcomes (n = 51) or they reported irrelevant outcomes like quality-of-life, mental status, respiratory outcomes, or stroke (n = 7). Finally, 33 studies were included, reporting 373,882 cancer patients[3-6,11-13,17,24-48].

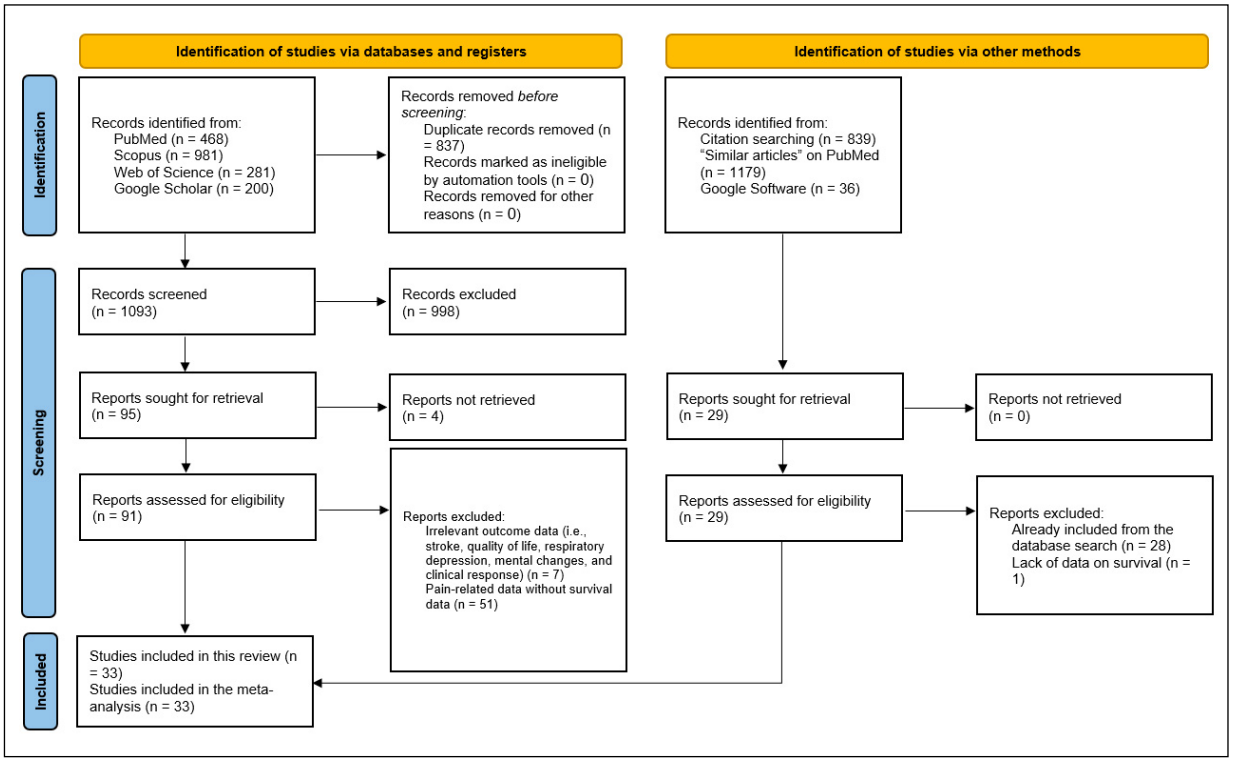

Figure 1. PRISMA diagram showing the results of the systematic literature search.

Baseline Characteristics of Included Studies

A total of 33 studies were included in the systematic review and meta-analysis (Table 1), which explored the impact of morphine consumption on cancer-related outcomes, including death, survival, and recurrence. These studies spanned across various countries and encompassed diverse care settings, including home-based (n = 16) and hospital-based (n = 17) environments. Most evidence was driven from the United States (n = 10) followed by Taiwan (n = 5). The studies varied in design, with most being retrospective chart reviews, cohort studies, and registry-based analyses. A small number of studies were prospective cohorts or randomized controlled trials.

The sample sizes of the included studies varied significantly, ranging from as few as 9 participants to over 336,000 participants, reflecting the wide range of study designs and populations examined. The cancer stages of the participants were generally not described, with some studies focusing specifically on advanced cancer stages. The majority of the studies did not involve surgical interventions, although a few did include surgery as part of the treatment protocol.

Table 1. Baseline characteristics of included studies discussing the impact of morphine consumption of cancer-related clinical data besides pain.

Author (YOP)	Design	YOI	Country	Cancer Stage	Care Setting	Surgery		Sample	MEDD (mg/day)		TMED (mg/day)		Route	Gender		Age	
						Yes/No	Name		M	SD	M	SD		M	F	Mean	SD
Krebs (2011)	Retrospective Registry (VA healthcare)	2000-2007	USA	ND	Home-based	No	-	20784	180	-	-	-	Oral	19745	1039	59	13
Oswald (2019)	Prospective cohort	2010-2015	UK	ND	Hospital-based	Yes	Thoracic surgery	70					IV	39	21	67.8	17.4
Liao (2023)	Retrospective chart review	2005-2018	Taiwan	ND	Hospital-based	No	-	336624	120.18	367.81	-	-	Oral	-	-	-	-
								217080	534.47	1556.38	-	-					
								123500	1073.91	3250.31	-	-					
								80618	1518.72	4806.72	-	-					
Portenoy (2006)	Prospective cohort (NHOP)	2001-2003	USA	ND	Home-based	No	-	248	200	-	65.7	45.6	IV	102	136	-	-
								59	200-400	-	906.3	3493		31	28		
								294	400-600	-	89.5	91.7		123	171		
								13	>600	-	2944	7159		4	9		
Maher (2014)	Retrospective chart review	2006-2008	USA	ND	Hospital-based	Yes	VATS	99	10	-	124	101	Oral	36	37	68	8
									3.3	-	-	-	IV				
Cronin-Fenton (2015)	Registry-based analysis	1996-2008	Denmark	ND	Home-based	No	-	1436	1-500	-	-	-	-	0	1436	-	-
									501-5000								
									>5000								
Montagna (2021)	Retrospective cohort	2010-2016	USA	ND	Home-based	No	-	1143	30	20	-	-	Oral	0	1143	54	14.5
Sun (2022)	Registry database (TCRD)	2008-2017	Taiwan	Early + Advanced	Home-based	No	-	1430	<180	-	-	-	IV	-	-	-	-
								286	≥180	-	-	-	IV				
Morita (2001)	Prospective cohort	1996-1998	Japan	ND	Hospital	No	-	133	136	329	-	-	Oral	-	-	-	-
Hu (2004)	Retrospective survey	2001-2002	Taiwan	ND	Home-based	No	-	136	44.69	52.33	-	-	Oral	77	59	61.5	13.9
Sathornviriyapong (2016)	Retrospective cohort	2013-2015	Bangkok	Advanced	Home-based	No	-	317	235	74.1	-	-	Oral	162	155	63	15.3
									155	48.9	-	-	IV				
									5	1.6	-	-	Subcutaneous				
Mercadante (2002)	RCT	1999-2000	Italy	Advanced	Home-based	No	-	156	-	-	246	26.1	Oral	12	10	64.6	15.8
Zylla (2014)	Retrospective cohort	2003-2010	USA	Advanced	Home-based	No	-	44	0.01-4.99	-	-	-	IV	205	4	63	14.5
								48	5-29.99	-	-	-					
								40	>30	-	-	-					
Allende-Perez (2022)	Retrospective chart review	2012-2018	Mexico	ND	Home-based	No	-	2691	20	12.37	-	-	Oral	2350	3281	59	14.8
Zylla (2013)	Registry-based analysis (Minneapolis VA Tumor Registry + VA Central Cancer Registry)	1995-2010	USA	Advanced	Home-based	No	-	113	150	-	-	-	Oral	113	0	-	-
Bercovitch (2004)	Retrospective chart review	1995-2000	Israel	ND	Home-based	No	-	154	<60	-	-	-	IV	72	82	-	-
								242	60-299	-	-	-	Oral	115	127		
								32	300-599	-	-	-		20	12		
								7	≥600	-	-	-		5	2		
Vecera (2023)	Retrospective chart review	2007-2020	Czech	Advanced	Hospital-based	Yes	Resection	48	90	17.2	-	-	Oral	24	24	63	18.5
Reddy (2017)	Post-hoc study	2008	USA	Advanced	Hospital-based	No	-	164	134	70	-	-	Oral	89	75	55.9	13.2
Wang (2015)	Retrospective cohort	2006-2011	China	ND	Home-based	No	-	136	200				IV	96	40	-	-
Smith (2019)	Retrospective cohort	2002-2012	USA	ND	Hospital-based	Yes	Resection	103	120	-	-	-	Intrathecal	84	19	61.6	9.7
Patino (2017)	Retrospective chart review	2003-2016	USA	ND	Hospital-based	Yes	Resection	268	100	-	-	-	Oral	189	79	60.5	15.3
Day (2012)	Retrospective cohort	2003-2010	UK	ND	Hospital-based	Yes	Resection	173	120	-	-	-	Oral	90	83	70	17.9
Merquiol (2013)	Retrospective cohort (propensity-score matched)	1984-2008	France	ND	Hospital-based	Yes	Resection	65	-	-	-	-	IV	61	4	58.6	11
Binczak (2013)	Post-hoc study	1990-1991	France	ND	Hospital-based	Yes	Resection	63	32	19	-	-	Subcutaneous	-	-	-	-
Azoulay (2011)	Retrospective cohort	2006-2007	Israel	Advanced	Hospital-based	No	-	9	0	-	-	-	Oral	4	5	-	-
								66	1-119	-	-	-		26	40		
								39	≥120	-	-	-		18	21		
Lim (2018)	Random cohort	2014	USA	Advanced	Home-based	No	-	390	102.5	181	-	-	Oral	-	-	-	-
Heinrich	Retrospective cohort	1995-2005	Germany	ND	Hospital-based	Yes	Resection	153	187	30.54	-	-	Oral	134	19	63.4	15.3
Chiang (2014)	Retrospective cohort	2007-2008	Taiwan	Advanced	Hospital-based	No	-	69	69.13	-	-	-	Oral	127	78	62.6	13
								144	71.5	-	-	-	IV				
								67	72.19	-	-	-	Transdermal				
Mercadante (2013)	Retrospective survey	2008-2009	Italy	Advanced	Home-based	No	-	201	106	77	-	-	Parenteral Oral	116	85	69	-
Wuethrich (2013)	Retrospective cohort	1994-2000	Switzerland	ND	Hospital-based	Yes	Resection	81	6-25	-	-	-	IV	81	0	63.83	15.9

Morphine administration routes differed across studies, with oral (n = 21) and intravenous (IV; n = 14) routes being the most commonly reported. The morphine equivalent daily dose (MEDD) and total morphine equivalent dose (TMED) also varied widely, with some studies reporting specific doses while others only provided ranges or did not report dose information at all. It ranged from as low as 0.01 to above 5000 mg. The demographic characteristics of the study populations indicated a broad age range, with mean ages typically ranging from the 50s to 70s.

Data regarding the number of cancer cases stratified by cancer type, along with the reported rate of metastasis, is reported in Table 2. Overall, 373,882 cancer patients were investigated, most of whom had non-specified cancer type (362114, 96.85%) followed by breast cancer (3434, 0.919%), colorectal cancer (2217, 0.592%), and lung cancer (1194, 0.319%), respectively. Meanwhile, skin cancer (10, 0.0026%), ovarian cancer (30, 0.0080%), and nervous system (10, 0.0026%) cancers were the least investigated types. Metastasis was reported by six studies[6,11,24,25,30,40], with an overall rate of 69.59% with varying rates based on the site of metastasis.

Table 2. The distribution of different cancer types and the rate of metastasis in studies discussing the impact of morphine on cancer-related survival.

Author (YOP)	Cancer Type																			Metastasis (%)					
	Lung	Oral	Liver	GI	Gynecological	Nervous System	Breast	Ovarian	Colorectal	Pancreas	Prostate	Urogenital	Stomach	Uncertain	Cervical/ Uterine	Hematological	Skin	H&N	Other/NS	Total	Bone	Liver	Lung	Brain	Other
Krebs (2011)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20784	-	-	-	-	-	-
Oswald (2019)	70	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liao (2023)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	336624	-	-	-	-	-	-
Portenoy (2006)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	307	-	-	-	-	-	-
Maher (2014)	99	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cronin-Fenton (2015)	-	-	-	-	-	-	1436	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Montagna (2021)	-	-	-	-	-	-	1143	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sun (2022)	300	-	252	-	-	-	12	30	168	132	36	-	126	-	-	-	-	126	1188	-	-	-	-	-	-
Morita (2001)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	133	-	-	-	-	-	-
Hu (2004)	23	-	19	27	-	-	-	-	16	12	-	-	11	3	8	-	-	4	45	-	47	33	31	20	55
Sathornviriyapong (2016)	57	-	-	127	-	-	22	-	-	-	-	34	-	-	-	-	-	43	34	89	-	-	-	-	-
Mercadante (2002)	4	-	2	4	-	-	2	-	-	2	-	8	-	-	-	-	-		2	-	-	-	-	-	-
Zylla (2014)	209	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Allende-Perez (2022)	-	-	-	-	-	-	678	-	547	-	-	-	662	-	508	482	-	-	2754	54	-	-	-	-	-
Zylla (2013)	-	-	-	-	-	-	-	-	-	-	113	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bercovitch (2004)	81	-	-	-	-	-	71	-	44	-	24	-	95	-	-	-	-	-	105	-	-	-	-	-	-
Vecera (2023)	-	-	-	-	-	-	-	-	-	71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Reddy (2017)	34	-	-	38	14	-	12	-	-	-	-	13	-	-	-	-	-	-	21	-	-	-	-	-	-
Wang (2015)	136	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Smith (2019)	-	-	103	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Patino (2017)	-	268	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Day (2012)	-	-	-	-	-	-	-	-	173	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Merquiol (2013)	-	-	-	65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Binczak (2013)	-	-	-	63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Azoulay (2011)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9	85.7	-	-	-	-	-
Lim (2018)	44	-	-	86	32	-	32	-	-	-	-	52	-	-	-	48	10	32	28	-	-	-	-	-	-
Heinrich	-	-	-	153	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chiang (2014)	38	-	31	26	-	-	9	-	21	12	-	22	9	-	-	-	-	33	25	61	71	38	39	16	-
Mercadante (2013)	53	-	8	43	-	-	17	-	-	17	-	32	-	-	-	-	-	-	31	-	-	-	-	-	-
Wuethrich (2013)		-	-	-	-	-	-	-	-	148	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cao (2014)	-	-	451	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wu (2019)	-	-	-	-	-	-	-	-	1248	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bengoechea (2010)	46	-	-	101	20	10	-	-	-	-	-	22	-	-	-	-	-	-	24	58.29	-	-	-	-	-
Pooled Rate	1194	268	866	733	66	10	3434	30	2217	394	173	183	903	3	516	530	10	238	362114	69.59	59	35.5	35	18	55

YOP: Year of Publication; GI: Gastrointestinal; NS: Not Specified; H&N: Head and Neck.

Methodological quality of included studies

The summary of the methodological quality of the included studies is provided in Table 3. Overall, most studies had good quality, while 10 studies[3,5,6,17,27,31,34,35,38,39] had fair quality (due to lack of confounding control through matching or regression models) and 1 study[29] had poor quality (due to lack of confounding control and inadequate follow-up period).

Table 3. A summary of the methodological quality of included studies using the Newcastle Ottawa Scale (NOS) for observational cohort studies.

Author (YOP)	Selection				Comparability	Outcome			Overall rating
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for confounders	Assessment of outcome	Enough follow-up period	Adequacy of follow-up of cohorts	
Krebs (2011)	*	*	*	*	-	*	*	*	Fair
Oswald (2019)	*	*	*	*	*	*	*	*	Good
Liao (2023)	*	*	*	*	*	*	*	*	Good
Portenoy (2006)	*	*	*	*	-	*	*	*	Fair
Maher (2014)	*	*	*	*	*	*	*	*	Good
Cronin-Fenton (2015)	*	*	*	*	*	*	*	*	Good
Montagna (2021)	*	*	*	*	-	*	*	*	Fair
Sun (2022)	*	*	*	*	*	*	*	*	Good
Morita (2001)	*	*	*	*	*	*	*	*	Good
Hu (2004)	*	*	*	*	*	*	*	*	Good
Sathornviriyapong (2016)	*	*	*	*	*	*	*	*	Good
Mercadante (2002)	*	*	*	*	-	*	*	*	Fair
Zylla (2014)	*	*	*	*	*	*	*	*	Good
Allende-Perez (2022)	*	*	*	*	*	*	*	*	Good
Zylla (2013)	*	*	*	*	*	*	*	*	Good
Bercovitch (2004)	*	*	*	*	-	*	*	*	Fair
Vecera (2023)	*	*	*	*	*	*	*	*	Good
Reddy (2017)	*	*	*	*	-	*	*	*	Fair
Wang (2015)	*	*	*	*	*	*	*	*	Good
Smith (2019)	*	*	*	*	*	*	*	*	Good
Patino (2017)	*	*	*	*	*	*	*	*	Good
Day (2012)	*	*	*	*	-	*	*	*	Fair
Merquiol (2013)	*	*	*	*	-	*	*	*	Fair
Binczak (2013)	*	*	*	*	*	*	*	*	Good
Azoulay (2011)	*	*	*	*	*	*	*	-	Good
Lim (2018)	*	*	*	*	*	*	*	*	Good
Heinrich	*	*	*	*	-	*	*	-	Poor
Chiang (2014)	*	*	*	*	-	*	*	*	Fair
Mercadante (2013)	*	*	*	*	-	*	*	*	Fair
Wuethrich (2013)	*	*	*	*	*	*	*	*	Good
Cao (2014)	*	*	*	*	*	*	*	*	Good
Wu (2019)	*	*	*	*	*	*	*	*	Good
Bengoechea (2010)	*	*	*	*	*	*	*	*	Good

YOP: year of publication.

Overall Survival

Subgroup analysis

The subgroup analysis revealed that morphine dose (p = 0.001), route of administration (p = 0.001), and follow-up time (p = 0.001) significantly modified the observed survival (Figure 2). In terms of morphine MEDD, low morphine dose was the most commonly investigated one followed by high doses. Very high doses were associated with the lowest survival rates of 13% [95% CI: 3-24%]. Meanwhile, low morphine dose resulted in the greatest survival of 41% [95% CI: 35-47%].

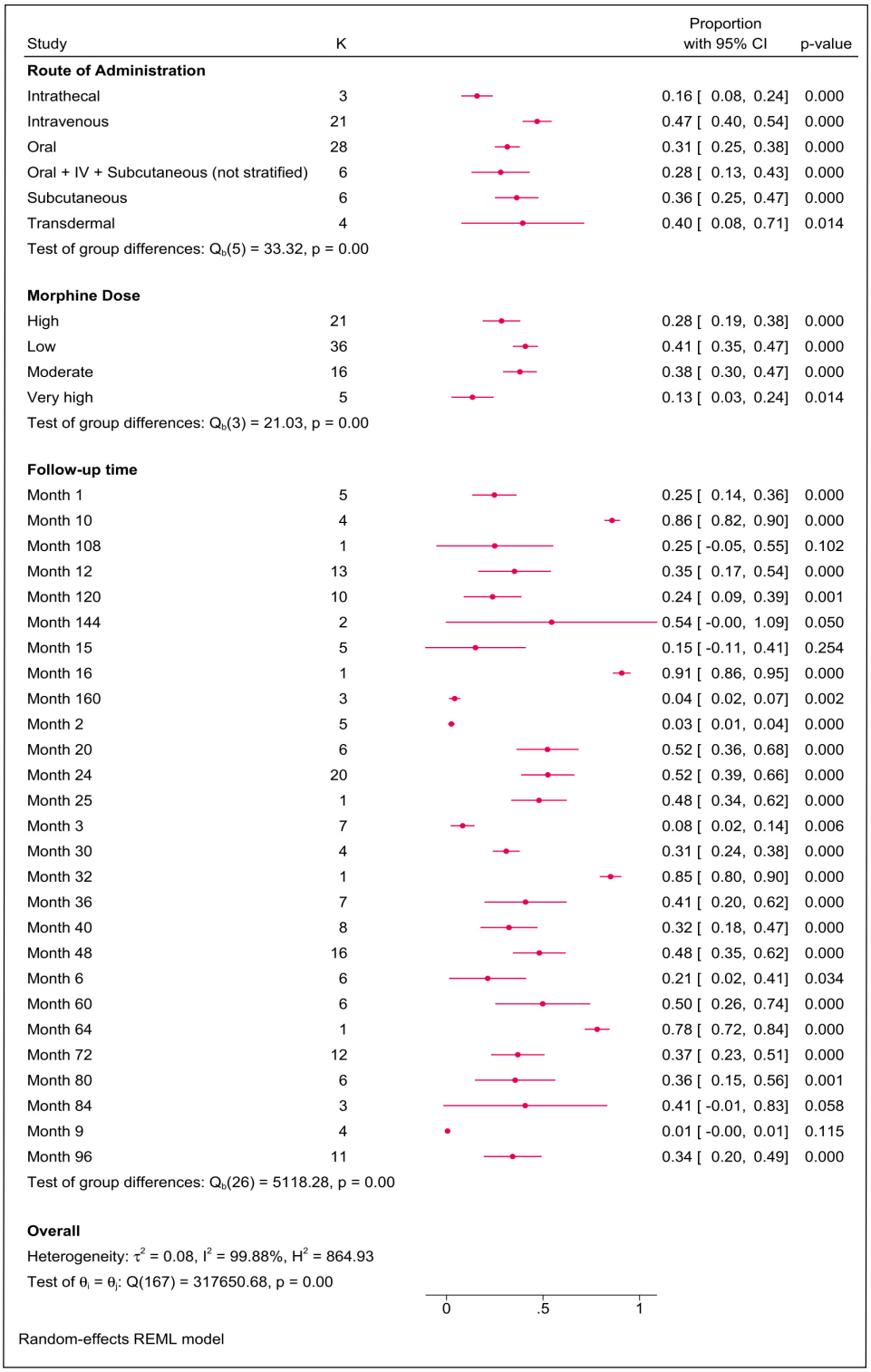

Figure 2. Forest plot showing the overall survival rate of cancer patients receiving morphine stratified by follow-up period and morphine dosage and route of administration.

Regarding the morphine route of administration, oral morphine was the most frequently reported route followed by intravenous administration. Intravenous morphine was associated with the greatest survival rate of 47% [95% CI: 40-54%] followed by transdermal [40%; 95% CI: 8-71%], subcutaneous [36%; 95% CI: 25-47%], and oral morphine [31%; 95% CI: 25-38%]. Intrathecal morphine resulted in the lowest survival [16%; 95% CI: 8-24%].

The rate of overall survival changed variably over time showing a slight negative trend over the whole follow-up time (Figure S1). The Galbraith plot showed 4 outliers from all analyzed subgroups (Figure S2), and there was no risk of publication bias (Figure S3) based on Egger's regression test (p = 0.43).

Pooled meta-analysis of Cox-proportional hazards models

The pooled meta-analysis of the Cox-proportional hazards models of the odds of survival with morphine consumption is shown in Figure 3. The morphine route of administration (p = 0.01) and follow-up period (p = 0.001) were the only determinants of the observed risk. Specifically, the intrathecal route was the only route to show a reduction in the odds of survival (HR = 0.65; 95% CI: 0.44-0.85). This reduced risk was only observed at 10 months (HR = 0.93; 95% CI: 0.90-0.96) and 40 months (HR = 0.75; 95% CI: 0.55-0.95).

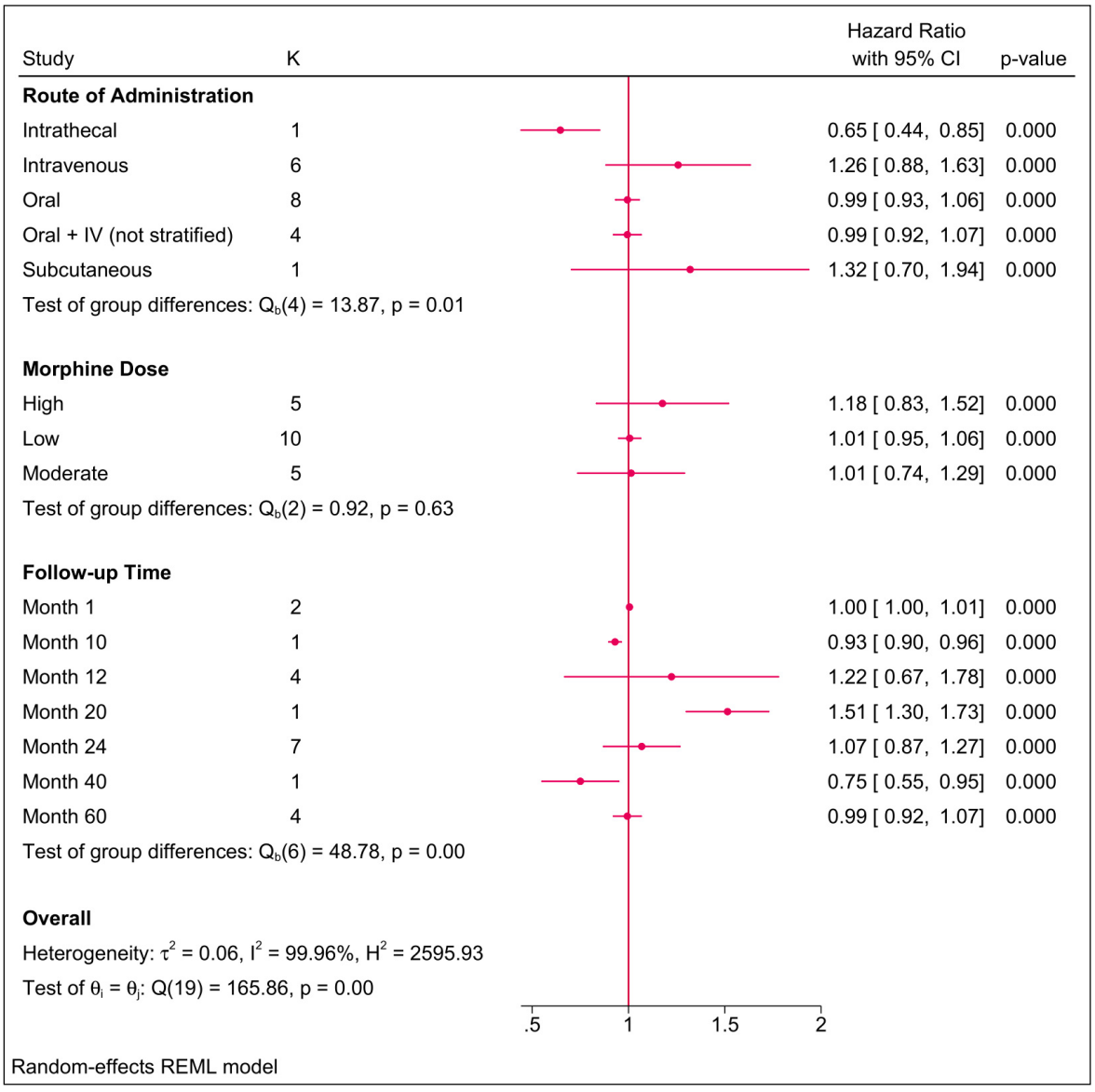

Figure 3. Forest plot of the Cox proportional hazards models investigating the odds of overall survival among cancer patients receiving morphine.

Meta-regression analysis

The meta-regression analysis revealed that neither the follow-up period nor the morphine dose were significant determinants of the observed risk (Table 4). However, the route of administration was the only significant determinant of the observed risk, with intravenous morphine showing greater odds of survival compared to oral one (coefficient = 0.163, p = 0.001). The model fit was poor (R^2 = 6.42%) and residual heterogeneity was substantial (I^2 = 99.87%).

Table 4. Meta-regression analysis of the determinants of overall suvival among cancer patients receiving morphine.

	Coefficient	SE	Z	*p*-value	Low CI	High CI
Follow-up (per month increase)	-0.00045	0.000612	-0.74	0.459	-0.00165	0.000747
Route of administration [Reference Group: Oral]						
Intravenous	0.163192	0.051293	3.18	**0.001**	0.06266	0.263724
Subcutaneous	0.028761	0.133994	0.21	0.83	-0.23386	0.291386
Transdermal	0.023019	0.147778	0.16	0.876	-0.26662	0.312657
Not stratified (oral, IV, SC)	-0.07654	0.121002	-0.63	0.527	-0.3137	0.160615
Intrathecal	-0.18674	0.172558	-1.08	0.279	-0.52494	0.151471
Morphine dose [Reference Group: Low Dose]						
Moderate	0.035923	0.057329	0.63	0.531	-0.07644	0.148287
High	-0.10569	0.062263	-1.7	0.09	-0.22772	0.016342
Very High	-0.16992	0.147982	-1.15	0.251	-0.45995	0.120123
constant	0.347506	0.054975	6.32	0	0.239756	0.455255

SE: standard error; CI: confidence interval; IV: intravenous; SC: subcutaneous

Mortality Rate

Subgroup analysis

The subgroup analysis revealed that morphine dose (p = 0.001), route of administration (p = 0.001), and follow-up time (p = 0.001) significantly modified the observed survival (Figure 4). In terms of morphine MEDD, a low morphine dose was the most commonly investigated one followed by a moderate dose. High morphine dose was associated with the highest death rate of 40% [95% CI: -2, 81%]. Although a very high dosage resulted in the lowest death rate of 11%, this finding was based only on one observation. Meanwhile, a moderate dose was associated with the next lowest death rate of 20% [95% CI: 9-30%].

Regarding the morphine route of administration, intravenous morphine was the most frequently reported route followed by oral administration. Oral and intravenous routes had quite similar death rates of 22% [95% CI: 9-35%] and 26% [95% CI: 19-34%], respectively.

The mortality rate changed variably over time showing a slight negative trend over the whole follow-up time (Figure S4). The death rate was highest in the early follow-up period and reached a plateau at 70 months. The Galbraith plot showed a heterogeneous distribution of effects across the regression line with no substantial outliers (Figure S5), and there was no risk of publication bias (Figure S6) based on Egger's regression test (p = 0.51).

Pooled meta-analysis of Cox-proportional hazards models

The pooled meta-analysis of the Cox-proportional hazards models of the risk of death with morphine consumption is shown in Figure 5. Morphine dose (p = 0.001) and follow-up period (p = 0.001) were the only determinants of the observed risk. Specifically, oral morphine revealed the highest mortality risk [HR = 16.09; 95% CI: 6.29, 25.89] followed by intravenous morphine [HR = 4.00; 95% CI: 1.29, 6.71]. This risk was only observed with high [HR = 28.80; 95% CI: 27.89, 29.71] and very high [HR = 27.89; 95% CI: 26.75, 29.03] doses of morphine. This imposed risk was observed during the time period from 6 to 60 months.

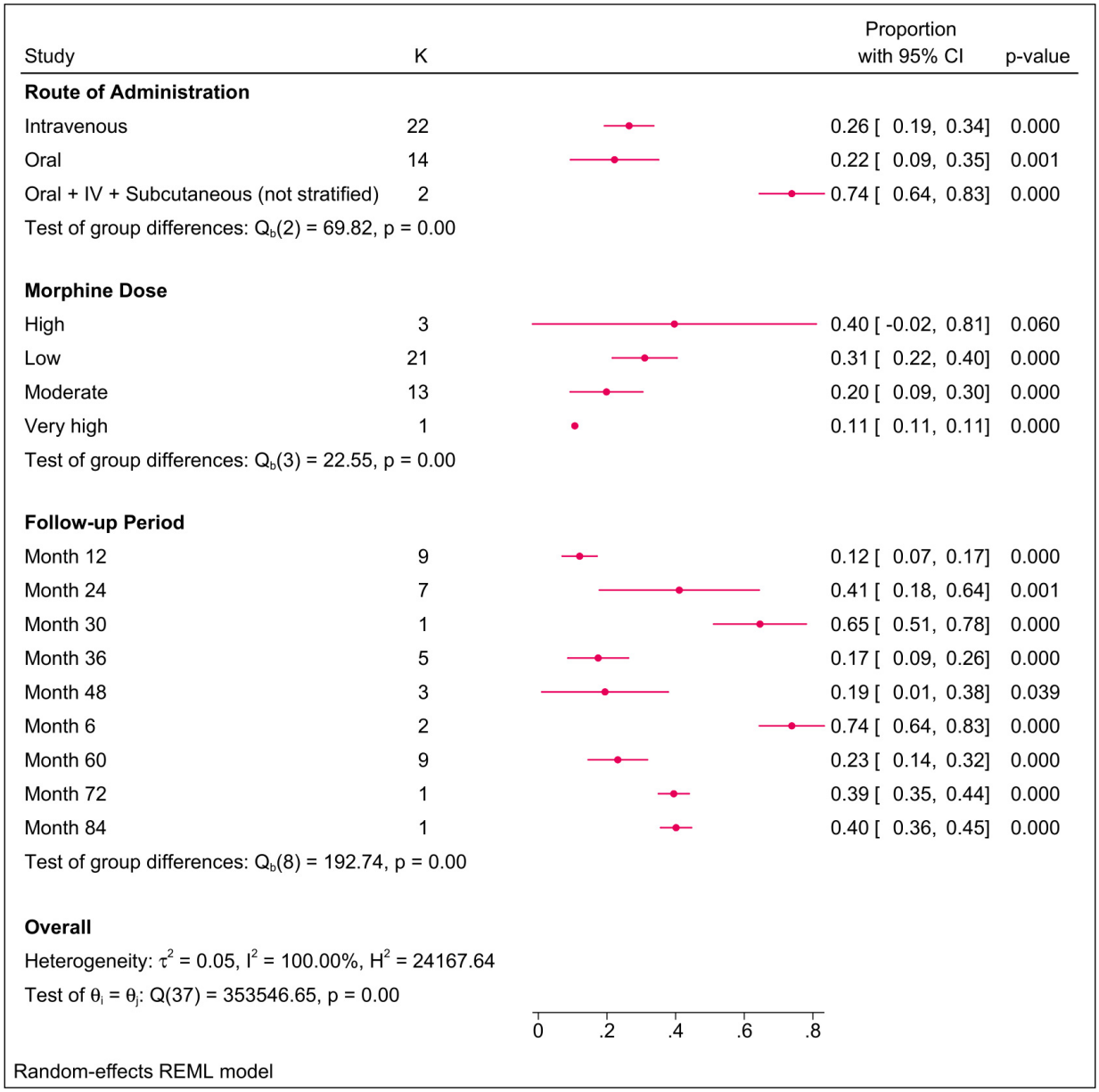

Figure 4. Forest plot showing mortality rate of cancer patients receiving morphine stratified by follow-up period and morphine dosage and route of administration.

Meta-regression analysis

The meta-regression analysis revealed that both the follow-up period and morphine dose were not significant determinants of the observed risk (Table 5). However, the route of administration was the only significant determinant of the observed risk, with combined oral, IV, and SC revealing higher risk compared to the oral route (coefficient = 0.531, p = 0.001). The model fit was poor (R^2 = 25.55%) and residual heterogeneity was substantial (I^2 = 99.99%).

Recurrence Rate

Subgroup analysis

The subgroup analysis revealed that morphine dose (p = 0.001), route of administration (p = 0.001), and follow-up time (p = 0.001) significantly modified the observed recurrence rate (Figure 6). Intravenous morphine was associated with the greatest recurrence rate of 38% [95% CI: 33-42%] followed by oral

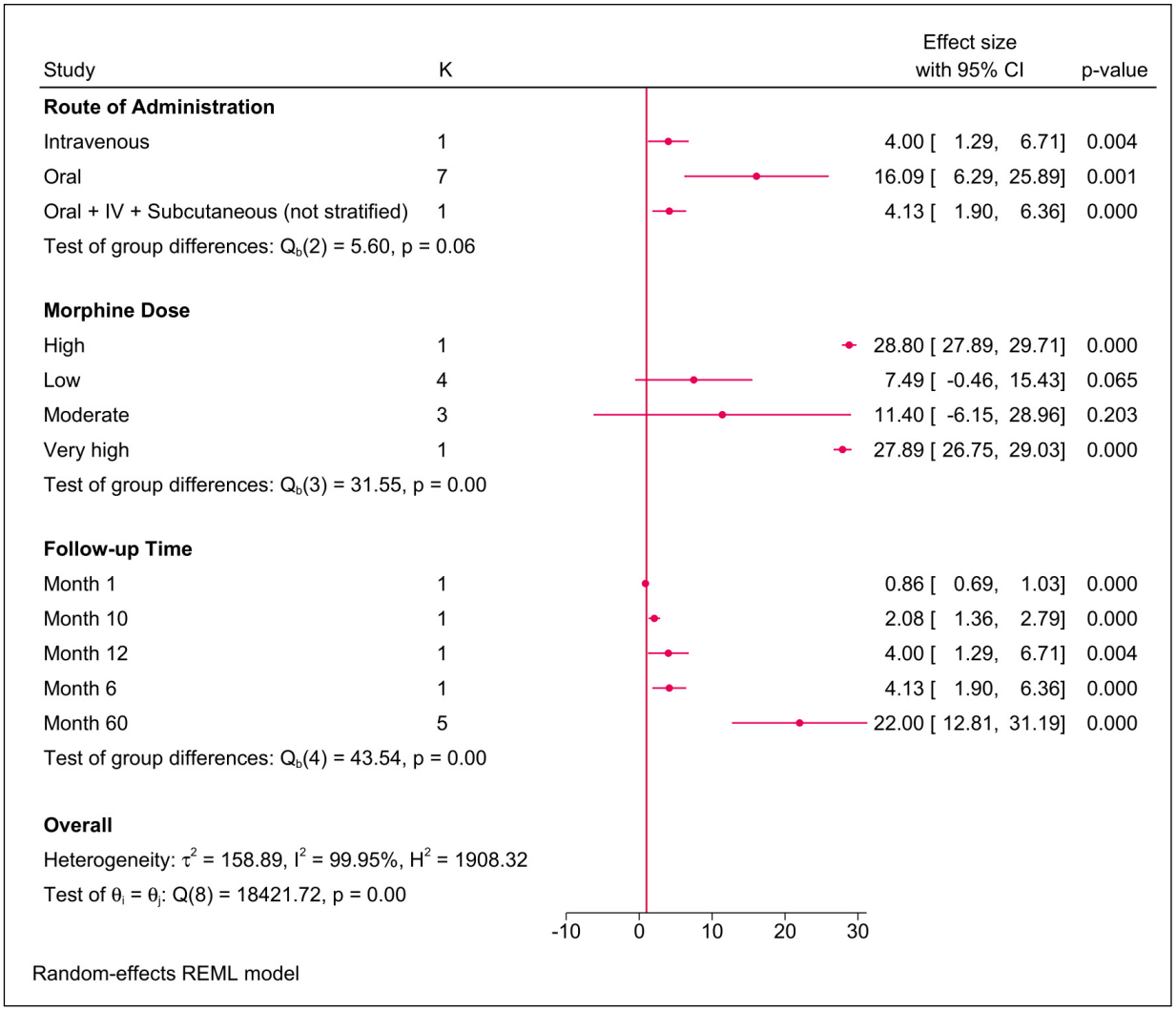

Figure 5. Forest plot of the Cox proportional hazards models investigating the risk of mortality among cancer patients receiving morphine.

Table 5. Meta-regression analysis of the determinants of mortality among cancer patients receiving morphine.

	Coefficient	SE	Z	*p*-value	Low CI	High CI
Follow-up (per month increase)	0.00118	0.001669	0.71	0.48	-0.00209	0.004452
Route of administration [Reference Group: Oral]						
Intravenous	-0.03535	0.080547	-0.44	0.661	-0.19322	0.12252
Not stratified (Oral, IV, SC)	0.531124	0.157781	3.37	0.001	0.221879	0.840369
Morphine dose [Reference Group: Low Dose]						
Moderate	-0.11906	0.079704	-1.49	0.135	-0.27527	0.037161
High	0.139004	0.123732	1.12	0.261	-0.10351	0.381515
Very High	-0.20114	0.165865	-1.21	0.225	-0.52623	0.123947
constant	0.265046	0.095712	2.77	0.006	0.077453	0.452639

SE: standard error; CI: confidence interval; IV: intravenous; SC: subcutaneous

morphine [28%; 95% CI: 22-34%]. Moderate doses had the greatest recurrence rate of 46% [95% CI: 38-54%], while low doses had the lowest rates [27%; 95% CI: 24-31%].

In terms of time, recurrence showed the highest rate during the early follow-up period with a constant progressive negative sleep over time (Figure S7). The death rate was highest in the early follow-up period and reached a plateau at 70 months. The Galbraith plot showed a heterogeneous distribution of effects across the regression line with no outliers (Figure S8). Publication bias assessment was not feasible, given the small sample size.

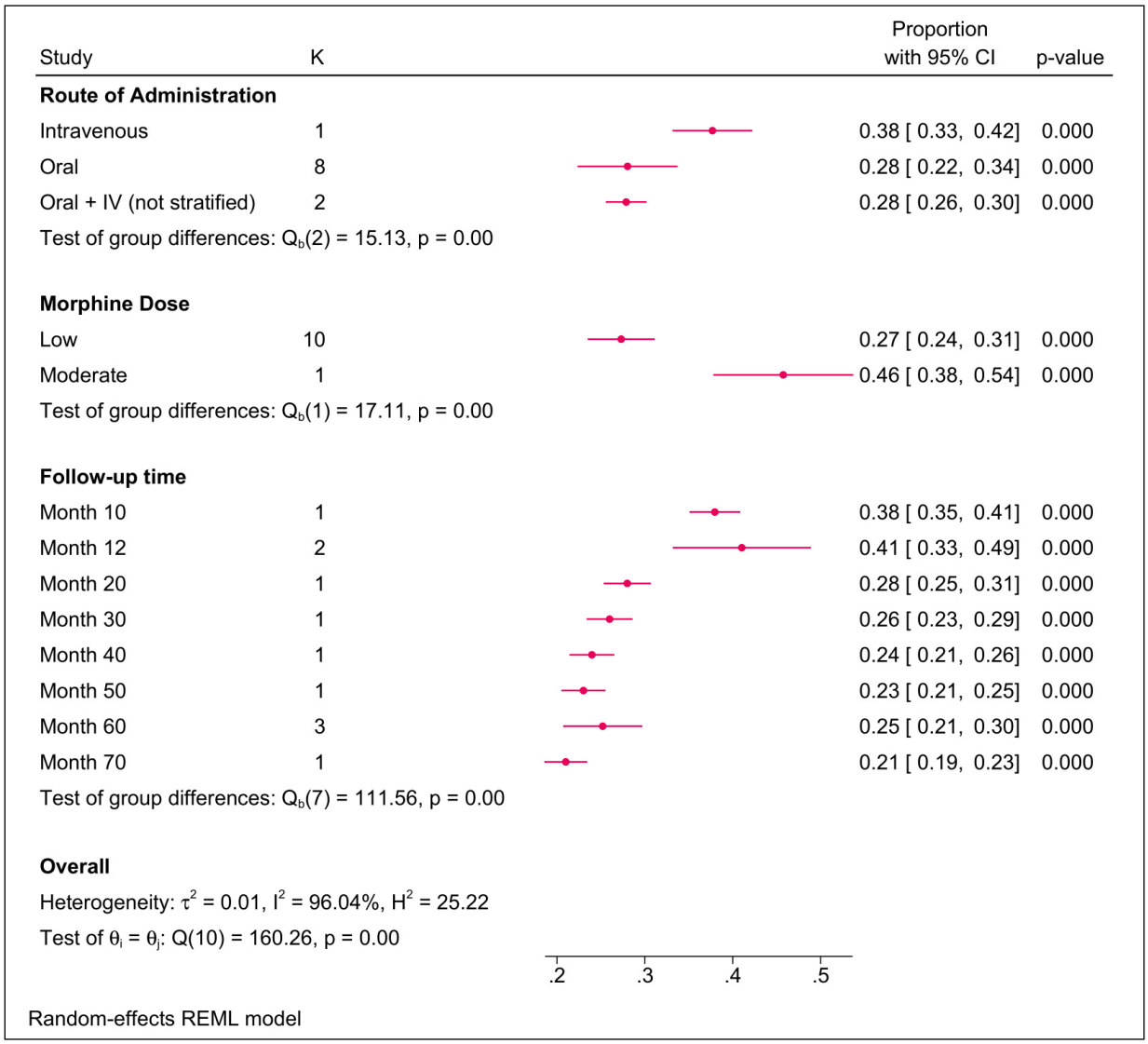

Figure 6. Forest plot showing the rate of recurrence of cancer patients receiving morphine stratified by follow-up period and morphine dosage and route of administration.

Meta-regression analysis

The meta-regression analysis revealed that all investigated factors were significant determinants of cancer recurrence (Table 6). Specifically, a one-month increase in the follow-up period reduced the risk of recurrence (coefficient = -0.0023, *p* =0.0001), and moderate morphine dose results in greater recurrence risk compared to low dosage (coefficient = 0.132, *p* = 0.0001).

Table 6. Meta-regression analysis of the determinants of cancer recurrence among cancer patients receiving morphine.

	Coefficient	SE	Z	*p*-value	Low CI	High CI
Follow-up (per month increase)	-0.00233	0.000539	-4.32	0.000	-0.00338	-0.00127
Route of administration [Reference Group: Oral]						
Intravenous	0.05217	0.038916	1.34	0.18	-0.0241	0.128445
Not stratified (oral, IV)	0.062849	0.028791	2.18	0.029	0.006421	0.119277
Morphine dose [Reference Group: Low Dose]						
Moderate	0.132747	0.051146	2.6	0.009	0.032502	0.232991
constant	0.352691	0.024304	14.51	0.000	0.305057	0.400326

SE: standard error; CI: confidence interval; IV: intravenous; SC: subcutaneous

DISCUSSION

This systematic review and meta-analysis aimed to evaluate the impact of morphine on cancer-related outcomes, specifically focusing on survival, death, and recurrence rates among cancer patients. The results of the study indicate a complex relationship between morphine administration and cancer prognosis, with significant variability observed across different doses, routes of administration, and follow-up periods.

Morphine and Cancer Survival

The analysis revealed that morphine dosage significantly influences survival outcomes, with very high doses being associated with the lowest survival rates. This finding aligns with previous literature suggesting that higher doses of opioids, including morphine, may have immunosuppressive effects, potentially facilitating tumor progression and metastasis[7]. The low survival rates observed with very high doses of morphine may be attributed to these biological effects, which could counteract the analgesic benefits of morphine in cancer patients.

Interestingly, the study also found that intravenous administration of morphine was associated with the highest survival rates, followed by transdermal, subcutaneous, and oral routes. This could be due to the pharmacokinetic advantages of intravenous administration[49], which allows for more controlled and efficient drug delivery. This could potentially minimize the systemic effects that could contribute to poor survival. However, the survival advantage of intravenous morphine needs to be interpreted cautiously, as it could also reflect patient selection biases. For instance, intravenous morphine might be administered to patients who are already receiving intensive care and monitoring, thus artificially inflating survival rates.

Morphine and Mortality

The analysis of mortality rates revealed a somewhat paradoxical finding: high doses of morphine were associated with the highest death rates, while very high doses were linked to the lowest death rates, albeit this latter finding was based on limited data. This paradox may be explained by the possibility that very high doses are administered in palliative care settings, where the primary goal is comfort rather than prolongation of life. In such contexts, the lower death rates might reflect the shorter time patients survive under such care, rather than an actual reduction in mortality risk.

Moreover, oral morphine was associated with a higher mortality risk compared to intravenous morphine, which is consistent with the idea that the route of administration plays a critical role in determining morphine's effects on cancer outcomes[50]. Oral morphine undergoes first-pass metabolism in the liver, which could lead to the production of metabolites that might be more harmful than the parent compound, thereby increasing mortality risk[51]. On the other hand, intravenous administration bypasses this process, which might account for its association with lower mortality[51].

Morphine and Cancer Recurrence

The recurrence analysis highlighted that moderate doses of morphine were linked to the highest recurrence rates, while low doses were associated with the lowest recurrence rates. This dose-response relationship suggests that morphine's impact on recurrence might be dose-dependent, with higher doses possibly promoting tumor recurrence. This could be due to the immunosuppressive effects of opioids, as previously mentioned[52], or through the activation of specific pathways that facilitate tumor cell survival and proliferation[53].

The finding that intravenous morphine was associated with the highest recurrence rates further complicates the narrative, as it contrasts with the survival analysis where intravenous morphine appeared beneficial. This discrepancy might be explained by the fact that survival and recurrence are not necessarily inversely related; a patient might survive longer with their disease in a managed state, only to experience a recurrence later[54]. This reinforces the idea that morphine's effects are multifaceted and may vary depending on the clinical context and the specific outcomes being measured.

Implications for Clinical Practice

The findings of this study have important implications for clinical practice. Firstly, they highlight the need for careful consideration of morphine dosage in cancer patients, as higher doses are associated with poorer outcomes in terms of survival and recurrence. Clinicians should weigh the analgesic bene-

fits of higher doses against the potential risks, particularly in patients with advanced cancer who may already be at higher risk of poor outcomes.

The study also underscores the importance of the route of administration, with intravenous morphine appearing to offer some survival benefits, though at the cost of higher recurrence rates. This suggests that intravenous morphine might be more appropriate for certain patient populations, particularly those requiring intensive pain management and monitoring, but less so for those at risk of tumor recurrence.

Finally, the results point to the need for more personalized approaches to morphine administration in cancer patients, where factors such as patient demographics, cancer type, and stage, as well as individual response to morphine, are taken into account. Future research should focus on elucidating the mechanisms underlying the dose- and route-dependent effects of morphine on cancer outcomes, which could lead to more targeted and effective pain management strategies in this population.

Limitations

Despite the strengths of this systematic review and meta-analysis, several limitations must be acknowledged. The included studies were highly heterogeneous in terms of design, population characteristics, and morphine administration protocols, which limits the generalizability of the findings. Additionally, the observational nature of most included studies raises the possibility of residual confounding, even though efforts were made to adjust for known confounders. Furthermore, some outcomes were not investigated such as cancer-specific survival, recurrence-free survival, and progression-free survival. Also, no cancer-specific data were available and this could account for the high level of residual heterogeneity in our meta-regression models which show that while the route of administration of morphine was a predictor of the observed risk, it accounted for a small proportion of the heterogeneity in these outcomes. Future studies should investigate other known risk factors of cancer survival, death, and recurrence and incorporate them into their regression models.

The meta-analysis was also limited by the lack of detailed reporting on certain variables, such as the precise timing of morphine administration relative to cancer treatment, which could have influenced the outcomes. Furthermore, the categorization of morphine doses based on MEDD, while necessary due to the variability in reporting, may have oversimplified the relationship between morphine and cancer outcomes, as it does not account for individual patient factors such as opioid tolerance or the presence of comorbidities.

CONCLUSIONS

This systematic review and meta-analysis provide evidence that morphine's impact on cancer-related outcomes is complex and influenced by both the dose and route of administration. While morphine remains a cornerstone of pain management in cancer patients, these findings suggest that higher doses and certain routes of administration may be associated with poorer outcomes in terms of survival and recurrence. Clinicians should consider these factors when prescribing morphine to cancer patients and strive to balance effective pain management with the minimization of potential risks. Further research is needed to better understand the mechanisms behind these effects and to develop more nuanced guidelines for the use of morphine in cancer care.

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Author contributions:
Georges Raymond Assaf: Conceptualization, Project administration, Supervision, Validation, Visualization, Methodology, Data analysis, and Writing – Original draft.
Rony Al Nawwar: Data curation, Methodology, Investigation, and Writing – revision and editing
Caroline Chahine: Data curation, Methodology, Investigation, and Writing – revision and editing
Krystel Malek: Data curation, Methodology, Investigation, and Writing – revision and editing
Hanane Barakat: Data curation, Validation, Methodology, Investigation, and Writing – revision and editing

Conflict of interest:
The authors declare that they have no conflict of interest to disclose.

Data availability statement:
The datasets generated during and/or analyzed during the current study are not publicly available due to privacy but are available from the corresponding author on reasonable request.

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