ORIGINAL ARTICLE / ÖZGÜN MAKALE

Predictors and outcomes of gastrointestinal complications after cardiac surgery: A systematic review and meta-analysis

Kalp cerrahi sonrası gastrointestinal komplikasyonların öngördürücüleri ve sonuçları: Sistematik inceleme ve meta-analiz

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ABSTRACT

Background: In this systematic review, we aimed to examine the risk factors and surgical outcomes of gastrointestinal complications using the meta-analysis techniques.

Methods: Studies involving patients with and without gastrointestinal complications after cardiac surgery were electronically searched using the PubMed database, Cochrane Library and Scopus database, between January 2000 and May 2022. Some studies on gastrointestinal complications examined only single gastrointestinal complication (only intestinal ischemia, only gastrointestinal bleeding or only liver failure). Studies evaluating at least three different gastrointestinal complications were included in the meta-analysis to reduce the heterogeneity. Cohort series that did not compare outcomes of patients with and without gastrointestinal complications, studies conducted in a country's health system databases, review articles, small case series (<10 patients) were excluded from the meta-analysis.

Results: Twenty-five studies (8 prospective and 17 retrospective) with 116,105 patients were included in the meta-analysis. The pooled incidence of gastrointestinal complications was 2.51%. Patients with gastrointestinal complications were older (mean difference [MD]=4.88 [95% confidence interval [CI]: 2.85-6.92]; p<0.001) and had longer cardiopulmonary bypass times (MD=17.7 [95% CI: 4.81-30.5]; p=0.007). In-hospital mortality occurred in 423 of 1,640 (25.8%) patients with gastrointestinal complications. In-hospital mortality was 11.8 times higher in patients with gastrointestinal complications (odds ratio [OR]=11.8 [95% CI: 9.5-14.8]; p<0.001).

Conclusion: The development of gastrointestinal complications after cardiac surgery is more commonly seen in patients with comorbidities. In-hospital mortality after cardiac surgery is 11.8 times higher in patients with gastrointestinal complications than in patients without.

Keywords: Cardiac surgical procedures, gastrointestinal tract, postoperative complications.

ÖΖ

Amaç: Bu sistematik derlemede, meta-analiz teknikleri kullanılarak gastrointestinal komplikasyonların risk faktörleri ve cerrahi sonuçları incelendi.

Çalışma planı: Kalp cerrahi sonrası gastrointestinal komplikasyon gelişen ve gelişmeyen hastaları içeren çalışmalar Ocak 2000 - Mayıs 2022 tarihleri arasında PubMed veri tabanı, Cochrane Kütüphanesi ve Scopus veri tabanı kullanılarak elektronik olarak tarandı. Gastrointestinal komplikasyonlara ilişkin bazı çalışmalarda yalnızca tek gastrointestinal komplikasyon (yalnızca bağırsak iskemisi, yalnızca gastrointestinal kanama veya yalnızca karaciğer yetmezliği) üzerine odaklanılmıştı. Çalışmalar arasındaki farklılığı azaltmak için en az üç farklı gastrointestinal komplikasyon değerlendiren çalışmalar meta-analize dahil edildi. Gastrointestinal komplikasyon gelişen veya gelişmeyen hastaların sonuçlarını karşılaştırmayan kohort serileri, ülkelerin sağlık sistemi veri tabanlarını kullanarak gerçekleştirilen çalışmalar, derleme makaleler ve küçük vaka serileri (<10 hasta) meta-analize dahil edilidi.

Bulgular: Meta-analize 116,105 hastayı içeren 25 çalışma (8'i prospektif ve 17'si retrospektif) dahil edildi. Gastrointestinal komplikasyonların havuzlanmış insidansı %2.51 idi. Gastrointestinal komplikasyon olan hastalar daha yaşlıydı (ortalama fark [MD]=4.88 [%95 güven aralığı [GA]: 2.85-6.92]; p<0.001) ve kardiyopulmoner baypas süreleri daha uzundu (MD=17.7 [%95 GA: 4.81-30.5]; p=0.007). Hastane içi mortalite gastrointestinal komplikasyonları olan 1,640 hastanın 423'ünde (%25.8) görüldü. Hastane içi mortalite, gastrointestinal komplikasyonları olan hastalarda 11.8 kat daha yüksekti (olasılık oranı [OR]=11.8 [%95 GA: 9.5-14.8]; p<0.001).

Sonuç: Kalp cerrahisi sonrası gastrointestinal komplikasyon gelişimi eşlik eden hastalıkları olan hastalarda daha fazla görülmektedir. Kalp cerrahisi sonrası hastane içi mortalite gastrointestinal komplikasyon gelişen hastalarda, gelişmeyen hastalara kıyasla, 11.8 kat fazladır.

Anahtar sözcükler: Kalp cerrahisi işlemleri, gastrointestinal sistem, ameliyat sonrası komplikasyonlar.

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Gastrointestinal (GI) organs are at risk for complex and multifactorial pathologies after cardiac surgery. The severity of GI complications (GICs) after surgery varies widely. Therefore, a clear consensus on the definition of GICs after cardiac surgery has not been developed. Intestinal ischemia, GI bleeding, hyperbilirubinemia or liver failure, splenic rupture, pancreatitis, cholecystitis, intestinal perforation, pseudomembranous enterocolitis, appendicitis or diverticulitis, intestinal obstruction, and ileus are among the GICs investigated in previous studies.^[1-25] It has been reported that visceral malperfusion is responsible for most GICs. Conditions such as prolonged hypotension, low cardiac output syndrome, or impaired regional blood flow cause visceral malperfusion.[26-28]

The diagnosis of GICs is often a clinical challenge. These complications may be overshadowed by sedation, severe cardiac, and pulmonary conditions. Delayed diagnosis of GICs can be often associated with catastrophic outcomes.^[29-31]

In the literature, there are studies performed for isolated acute mesenteric ischemia and isolated hyperbilirubinemia after cardiac surgery.^[32-34] In this systematic review, we aimed to examine the risk factors and surgical outcomes of GICs using the metaanalysis techniques.

MATERIALS AND METHODS

Literature search strategy

Electronic searches were performed using the PubMed database (United States National Library of Medicine), the Cochrane Library, and Scopus (Elsevier), selecting a date range from January 2000 to May 2022. The meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^[35,36] The terms "cardiac surgery" and "gastrointestinal complications" or "intestinal ischemia" or "mesenteric ischemia" or "gastrointestinal bleeding" or "hyperbilirubinemia" or "liver failure" or "splenic rupture" or "pancreatitis" or "cholecystitis" or "intestinal perforation" or "pseudomembranous enterocolitis" or "appendicitis" or "diverticulitis" or "intestinal obstruction" or "ileus" were used as keywords to find publications conducted in humans to have the most effective search results. In addition, the reference list of the selected articles was checked to identify potentially relevant articles. Duplicate articles were removed. All searches were screened independently by two different researchers. In case of differences between searches, another researcher was consulted for scanning security.

Study design and selection criteria

Only articles written in English were included in the meta-analysis. Studies eligible for this metaanalysis included patients who developed GICs after cardiac surgery. Some studies on GICs examined only single GIC (i.e., only intestinal ischemia or only GI bleeding or only liver failure). However, we included studies that evaluated at least three different GICs to increase similarity across GICs. Cohort series that did not compare the results of groups with or without GICs were excluded. Studies conducted in a country's health system databases were also excluded. In addition, review articles, case reports, small case series (<10 patients), Letters to the Editor, conference presentations, editorials, and how-to-do-it articles were excluded. This study is not registered in the International Prospective Register of Systematic Reviews (PROSPERO).

Data extraction

Demographic, operative, and outcome data were obtained from the main texts, tables, and figures of the relevant studies. The matched data from studies where propensity score matching was applied to preoperative variables were not included in the meta-analysis. Two independent researchers reviewed the studies and collected the data. The authors of included trials were contacted when necessary to clarify data and identify multiple publications. In the event of data inconsistency, the data were re-evaluated by another researcher and eventually a consensus was reached among the authors.

Preoperative demographic data, age, sex, atrial fibrillation (AF), hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), history of cerebrovascular disease (CVD), and dialysis-dependent chronic renal failure (DD-CRF) data were obtained from the relevant studies. As operative data, we collected the history of prior cardiac surgery (cardiac reoperation), emergency surgery requirement, aortic cross-clamp (ACC) time, cardiopulmonary bypass (CPB) time, and re-exploration for bleeding.

The primary outcome was defined as hospital mortality, which was defined as mortality occurring within 30 days postoperatively or without discharge. Secondary postoperative outcomes included the development of acute renal failure (ARF), new-onset AF, sepsis, peri- or postoperative myocardial infarction, postoperative stroke, and length of hospital stay.

Statistical analysis

Statistical analysis was performed using the R version 4.0.3 software (The R Foundation for Statistical Computing, Vienna, Austria). For binary variables, the odds ratio (OR) was calculated with a 95% confidence interval (CI) for proportions. A weighted mean difference was calculated with a 95% CI for means. Heterogeneity was examined using the Cochran's Q test, as well as the inconsistency index (I^2) statistic. The I^2 was used to measure the degree of heterogeneity: 0% to 30%, marginal heterogeneity; 30% to 50%, moderate heterogeneity; 50% to 75%, substantial heterogeneity and 75% to 100%, considerable heterogeneity. A fixed effect model was generated if I^2 was $\leq 30\%$, while a random effect model was generated if I^2 was >30%.^[37,38] Forest plots were created for primary and secondary outcomes. A funnel plot was also used to examine publication bias in the primary outcome. The Harbord test was used to evaluate the evidence for asymmetry in the funnel plot.^[39] A p value of < 0.05 was considered statistically significant.

RESULTS

Figure 1 shows the literature selection process. A total of 1,009 articles were identified through databases and reference lists of the selected articles. After the duplicate articles were removed, the titles and abstracts of 484 articles were reviewed. After

reviewing the abstracts and titles of the articles, the full texts of 88 articles thought to be relevant to the subject were evaluated. Of the 88 studies whose full texts were reviewed, 63 were excluded using the exclusion criteria. Some examples of excluded studies are studies that examined only single GIC,^[40-42] series that did not compare outcomes of patients with and without GICs.^[43,44] and studies conducted in a country's health system databases.^[45] Finally, a total of 25 studies were used in the meta-analysis.^[1-25] Due to the subject of the meta-analysis, all included articles were observational studies (8 prospective and 17 retrospective). For this meta-analysis, data were provided from a total of 116,105 patients, 2,910 of whom were diagnosed with GICs after cardiac surgery. The pooled incidence of GICs was 2.51%. Table 1 summarizes the characteristics of the included studies. The GICs investigated in the included studies are summarized in Table 2.

Table 3 shows the meta-analysis of the included studies. Patients with GICs were statistically significantly older than patients without GICs (mean difference [MD]=4.88 [95% CI: 2.85-6.92]; p<0.001; Figure 2). The GICs risk after cardiac surgery did not significantly differ by sex (OR: 0.91 [95% CI: 0.77-1.08]; p=0.291). Also, the rate of HT, DM, DD-CRF, COPD, PVD, CVD, and AF was statistically significantly higher in patients with GICs after cardiac surgery.

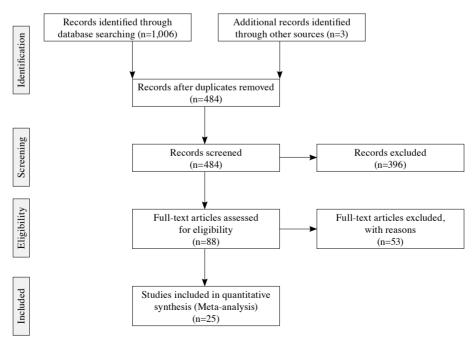


Figure 1. Flow chart of the study.

The development of GICs was statistically significantly higher by 2.2 times in patients with a history of previous cardiac surgery (OR: 2.18 [95% CI: 1.42-3.36]; p<0.001). Emergency surgery increased the development of GICs (OR: 2.64 [95% CI: 1.76-3.97]; p<0.001). The CBP time was statistically significantly longer in patients with GICs (MD=17.7 [95% CI: 4.81-30.5]; p=0.007; Figure 3). There was no statistically significant difference between the ACC times between patients with and without GICs (MD=5.92 [95% CI: -3.13-14.96]; p=0.200). Re-exploration for bleeding

was statistically significantly 4.3 times higher in patients with GICs (OR: 4.30 [95% CI: 2.84-6.49]; p<0.001).

Eighteen studies collected in-hospital mortality data. In-hospital mortality occurred in 423 of 1,640 (25.8%) patients with GICs. Hospital mortality was statistically significant, and it was 11.8 times higher in patients with GICs compared to patients without GICs (OR: 11.8 [95% CI: 9.5-14.8]; p<0.001; Figure 4). The Harbord test^[39] did not indicate a publication bias present for in-hospital mortality (p=0.12). Funnel plots

Study	Year	Study type	Type of cardiac surgeries	GI complications	No GI complications
McSweeney et al. ^[1]	2004	POS	All cardiac surgeries	133	2,284
D'Ancona et al. ^[2]	2003	POS	All cardiac surgeries	129	10,929
Viana et al. ^[3]	2013	POS	All cardiac surgeries	61	5,321
Grus et al. ^[4]	2014	ROS	All cardiac surgeries	75	5,884
Hess et al. ^[5]	2021	ROS-PSM	All cardiac surgeries	246	10,039
Golitaleb et al. ^[6]	2019	ROS	All cardiac surgeries	36	764
Andersson et al. ^[7]	2005	POS	All cardiac surgeries (without beating heart and transplant surgeries)	47	6,069
Bolcal et al. ^[8]	2005	ROS	All cardiac surgeries	128	13,416
Gulkarov et al. ^[9]	2014	ROS	Mitral valve surgeries (with or without CABG or other heart valves)	13	552
Marsoner et al. ^[10]	2019	ROS-PSM	All cardiac surgeries	101	101
Yoshida et al. ^[11]	2005	ROS	Isolated CABG - On pump	17	532
Ibrahimi et al. ^[12]	2019	ROS	All cardiac surgeries	34	1,990
Vassiliou et al. ^[13]	2008	ROS	All cardiac surgeries	33	3,691
Geissler et al. ^[14]	2006	ROS	All cardiac surgeries	65	1,057
Filsoufi et al. ^[15]	2007	ROS	All cardiac surgeries (without transplant surgeries)	51	4,768
Zacharias et al. ^[16]	2000	ROS	All cardiac surgeries	86	4,377
Vohra et al. ^[17]	2015	POS	CABG	65	2,255
Raja et al. ^[18]	2003	POS	CABG	18	482
Guler et al. ^[19]	2011	ROS	Isolated CABG - Off pump	19	95
Elgharably et al. ^[20]	2021	ROS	All cardiac surgeries	1,037	28,872
Byhahn et al. ^[21]	2001	POS	All cardiac surgeries	23	1,093
Recht et al. ^[22]	2004	POS	All cardiac surgeries	66	329
Haywood et al. ^[23]	2020	ROS	All cardiac surgeries	280	5,790
Khan et al. ^[24]	2006	ROS	All cardiac surgeries	112	484
Aithoussa et al. ^[25]	2017	ROS	All cardiac surgeries	35	2,021

Table 1. Characteristics of included studies

GI: Gastrointestinal; POS: Prospective observational study; ROS: Retrospective observational study; PSM: Propensity score matching; CABG: Coronary artery bypass grafting.

	GIC	No GIC	Mesenteric ischemia	Hyperbilirubinemia and liver failure	Gastrointestinal bleeding	Pancreatitis	Cholecystitis	Intestinal perforation	Pseudomembranous enterocolitis and colitis	Appendicitis or diverticulitis	Intestinal obstruction	lleus	Splenic rupture
McSweeney et al. ^[1]	133	2,284	*	*	*	*	*	*					
D'Ancona et al. ^[2]	129	10,929	*		*	*	*	*	*	*	*		
Viana et al. ^[3]	61	5,321	*	*	*	*	*	*	*		*	*	
Grus et al. ^[4]	75	5,884	*		*	*	*						
Hess et al. ^[5]	246	10,039	*	*	*	*	*		*			*	
Golitaleb et al. ^[6]	36	764	*	*	*	*	*	*				*	
Andersson et al. ^[7]	47	6,069	*	*	*	*	*	*				*	
Bolcal et al. ^[8]	128	13,416	*	*	*	*	*	*		*		*	
Gulkarov et al. ^[9]	13	552	*		*		*			*			
Marsoner et al. ^[10]	101	101	*		*	*	*	*				*	
Yoshida et al. ^[11]	17	532	*		*	*		*	*				
Ibrahimi et al. ^[12]	34	1,990	*	*	*	*	*	*		*			
Vassiliou et al. ^[13]	33	3,691	*	*	*	*							
Geissler et al. ^[14]	65	1,057	*		*	*	*	*				*	
Filsoufi et al. ^[15]	51	4,768	*		*			*					
Zacharias et al. ^[16]	86	4,377	*	*	*	*	*	*				*	
Vohra et al. ^[17]	65	2,255	*	*	*	*	*		*			*	
Raja et al. ^[18]	18	482	*	*	*	*	*	*	*				
Guler et al. ^[19]	19	95	*		*	*	*	*					*
Elgharably et al. ^[20]	1,037	28,872	*	*	*	*			*				*
Byhahn et al. ^[21]	23	1,093	*	*	*		*		*				*
Recht et al. ^[22]	66	329	*		*	*		*			*		
Haywood et al. ^[23]	280	5,790	*	*	*	*	*		*			*	
Khan et al. ^[24]	112	484	*		*	*	*	*			*		
Aithoussa et al. ^[25]	35	2,021	*	*	*	*	*						

GICs: Fastrointestinal complications.

for in-hospital mortality is shown in Figure 5. Acute renal failure, new-onset AF, myocardial infarction, stroke, and sepsis were statistically significantly more frequent in patients with GICs in the postoperative period. The length of hospital stay of patients with GIC was statistically significantly longer than that of

Preoperative data		Estimate	ate	р	Number of studies	Number of patients	Number of total	Tau ²	P(%)
	OR	MD	95% CI	i.	combined	combined	events		
Age (year) ^[2,5,8,9,12-17,19,21,22,24,25]		4.88	2.85-6.92	<0.001	15	58,201	*	13.9	86%
$Female^{[2-6,7-9,11-21,23-25]}$	0.91		0.77-1.08	0.291	21	112,291	35,492	0.07	64%
Hypertension ^[3,5,7-9,11,12,14-16,18,23,25]	1.56		1.12-2.16	0.008	17	89,029	55,555	0.35	86%
Diabetes mellitus ^[2-4,7-9,11,12,14-25]	1.50		1.18-1.90	<0.001	20	98,677	22,494	0.19	73%
DD-CRF ^[7,14,16,19,20,22,23]	2.89		1.02-8.21	0.045	7	48,189	1,977	1.45	94%
COPD ^[3,5,7,9,11,12,14-25]	1.87		1.70-2.04	<0.001	19	91,945	15,250	0.001	0%0
PVD ^[2-5,7,8,12,14-20,23-25]	2.28		1.87-2.77	<0.001	17	106,337	13,862	0.08	57%
CVD(3.5.8.9.11,12.14-17.19.20,24]	2.38		1.44-3.92	<0.001	13	75,692	8,669	0.66	82%
Atrial fibrillation ^[5,7,9,16,18,20,21,23-25]	1.80		1.57-2.08	<0.001	10	61,676	10,805	0.01	39%
Operative data									
Cardiac reoperation ^[2,4,5,7,8,1,3-16,21,21,23,24]	2.18		1.42-3.36	<0.001	13	98,781	12,163	0.48	93%
Emergency surgery ^[3,5,7,8,11,12,14,16,19,21,24]	2.64		1.76-3.97	<0.001	14	54,090	3,435	0.41	70%
ACC time, min ^[2,5,7,8,9,11,12,14,16,19,25]		5.92	-3.13-14.96	0.200	11	51,896	*	207.4	87%
CPB time, min ^[2,7,8,9,11,12,14,15,19,22,25]		17.7	4.81-30.5	0.007	11	42,006	*	396.3	82%
Re-exploration for bleeding ^[2-57,8,10,12,14,15,17,19,20,22,23,25]	4.30		2.84-6.49	<0.001	16	101,375	3752	0.53	84%
Operative outcomes									
Hospital mortality ^(1,10,14,17,21,23,25)	11.8		9.5-14.8	<0.001	18	78,689	2,756	0.12	63%
Acute renal failure ^[2-57,8,15,19,20,25]	11.3		7.1-17.8	<0.001	10	89,242	3,265	0.45	88%
New-onset $AF^{[3.579,20,23]}$	2.09		1.73-2.51	<0.001	7	64,286	14,085	0.02	55%
Myocardial infarction ^[1-4,7,10,15]	2.81		1.51-5.22	0.001	7	35,953	978	0.37	58%
Stroke ^[1,5,7,8,15,22,23]	4.07		2.36-7.02	<0.001	10	66,045	1,864	09.0	81%
Sepsis ^[2-57,10]	9.32		4.31-20.2	<0.001	9	39,002	384	0.65	73%
Hospital stay, day ^[1,6,8,16,17]		16.1	10.6-21.6	<0.001	S	23,544	*	33.4	91%

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										Weight	Weight
Study	GIC	Mean	SD	No- GIO	Mean	SD	Mean Difference	MD	95%-CI	(common)	(random)
D'Ancona ²	129	67	11	10929	63	11	1 4	4	[2.09; 5.91]	10.0%	7.3%
Hess ⁵	246	71	11	10039	67	11	1 🛋	4	[2.61; 5.39]	18.9%	7.5%
Bolcal ⁸	128	67	10	13416	63	11		4	[2.26; 5.74]	12.1%	7.3%
Gulkarov ⁹	13	68	12	552	65	14		3	[-3.63; 9.63]	0.8%	4.3%
Ibrahimi ¹²	34	70	9	1990	54	9		16	[12.95; 19.05]	3.9%	6.6%
Vassiliou ¹³	33	65	8	3691	63	3	- 	2	[-0.73; 4.73]	4.9%	6.8%
Geissler ¹⁴	65	65	11	1057	65	11		0	[-2.76; 2.76]	4.8%	6.8%
Filsoufi ¹⁵	51	69	11	4768	63	14	- [a -	6	[2.96; 9.04]	3.9%	6.6%
Zacharias ¹⁶	86	71	10	4377	63	11	- <u></u> -	8	[5.86; 10.14]	8.0%	7.2%
Vohra ¹⁷	65	69	8	2255	65	10	- 	4	[2.01; 5.99]	9.3%	7.2%
Guler ¹⁹	19	68	6	95	60	8	<u></u>	8	[4.86; 11.14]	3.7%	6.6%
Byhahn ²¹	23	65	10	1093	66	8		-1	[-5.11; 3.11]	2.2%	5.9%
Recht ²²	66	71	8	329	66	11	- 	5	[2.73; 7.27]	7.1%	7.1%
Khan ²⁴	112	68	10	484	66	11	<u> _ _</u> }	2	[-0.10; 4.10]	8.3%	7.2%
Aithoussa ²⁵	35	56	13	2021	48	14		8	[3.65; 12.35]	1.9%	5.7%
Common effect mod	el 1105			57096			÷.	4.59	[3.99; 5.20]	100.0%	
Random effects mod	del						-	4.88	[2.85; 6.92]		100.0%
Heterogeneity: $I^2 = 86\%$	$\tau^2 = 13.8$	615, p <	0.01								
U ,							-15 -10 -5 0 5 10 15				

Figure 2. Forest plot showing weight-for-age.

GIC: Gastrointestinal complications; SD: Standard deviation; MD: Mean difference; CI: Confidence interval.

Study	GIC Mean	SD	No- GIC Mean	SD	Mean Difference	MD	95%-CI	Weight (common) (Weight random)
D'Ancona ² Andersson ⁷ Bolcal ⁸ Gulkarov ⁹ Yoshida ¹¹ Ibrahimi ¹² Geissler ¹⁴ Zacharias ¹⁶ Guler ¹⁵ Recht ²² Aithoussa ²⁶	129 107 47 129 128 103 13 138 17 102 34 125 65 114 86 137 19 67 66 127 35 125	41 56 46 60 31 52 56 77 21 62 74	10929 91 6069 102 13416 87 552 114 1990 93 1057 93 4377 94 95 48 329 110 2021 100	39 43 42 48 151 48 45 44 14 84 41		27.00 16.00 24.00 -46.00 32.00 21.00	[-8.86; 56.86] [-65.54; -26.46] [14.39; 49.61] [7.12; 34.88] [26.67; 59.33] [9.15; 28.85] [-0.50; 34.50]	28.2% 5.5% 22.3% 1.3% 3.7% 4.6% 7.4% 5.3% 14.7% 4.7% 2.4%	10.5% 9.3% 10.4% 6.3% 9.0% 9.6% 9.2% 10.2% 9.0% 7.8%
Common effect model Random effects mode Heterogeneity: $I^2 = 82\%$, τ	l	< 0.01	41367		-60 -40 -20 0 20 40 60		[13.87; 21.42] [4.81; 30.51]	100.0% 	 100.0%

Figure 3. Forest plot for cardiopulmonary bypass time.

GIC: Gastrointestinal complications; SD: Standard deviation; MD: Mean difference; CI: Confidence interval.

Study	Mortalit	y GIC	Mortalit	y No- GIC	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
McSweeney ¹	26	133	64	2284	1 4	8.43	[5.14; 13.83]	8.3%	6.9%
D'Ancona ²	29	129	431	10929		7.06	[4.62; 10.80]	11.5%	7.5%
Viana ³	20	61	174	5321	-	14.43	[8.28; 25.15]	3.9%	6.3%
Grus₄	23	75	169	5884	 	14.96	[8.95; 25.01]	4.3%	6.7%
Hess⁵	61	246	270	10039		11.93	[8.72; 16.32]	14.3%	8.6%
Golitaleb	4	36	10	764	- + -	9.43	[2.80; 31.68]	1.2%	2.5%
Andersson ⁷	13	47	163	6069	-	13.85	[7.18; 26.75]	2.7%	5.4%
Bolcal [®]	18	128	328	13416	 {	6.53	[3.92; 10.88]	7.8%	6.7%
Gulkarov [®]	2	13	19	552	⊢ •+	5.10	[1.06; 24.63]	1.1%	1.7%
Marsoner ¹⁰	21	101	5	101	- 	5.04	[1.82; 13.97]	5.8%	3.3%
Geissler ¹⁴	14	65	32	1057		8.79	[4.42; 17.50]	4.3%	5.2%
Filsoufi ¹⁵	17	51	204	4768	- ÷	11.19	[6.15; 20.36]	4.2%	5.9%
Zacharias ¹⁶	26	86	109	4377		16.97	[10.31; 27.92]	4.3%	6.8%
Vohra ¹⁷	14	65	34	2255		17.93	[9.07; 35.45]	2.2%	5.3%
Byhahn ²¹	20	23	30	1093		236.22	[66.57; 838.28]	0.2%	2.4%
Recht ²²	20	66	15	329	- <u> </u>	9.10	[4.35; 19.03]	5.1%	4.8%
Haywood ²³	78	280	161	5790	+	13.50		15.8%	8.7%
Aithoussa ²⁵	17	35	115	2021		15.65	[7.86; 31.18]	3.0%	5.2%
Common effect model Random effects model Heterogeneity: $I^2 = 63\%$, τ^2		1640 ס < 0	01	77049		11.36 11.83		100.0% 	 100.0%
		-			0.01 0.1 1 10	100			

Figure 4. Forest plots for in-hospital mortality.

GIC: Gastrointestinal complications; CI: Confidence interval.

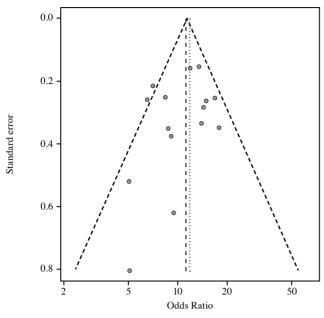


Figure 5. Funnel plot for in-hospital mortality.

patients without GICs (MD=16.1 [95% CI: 10.6-21.6]; p<0.001).

DISCUSSION

The two most striking results of this study are the following: (*i*) following cardiac surgery, 25.8% of GIC patients died in the hospital and (*ii*) the development of GICs after cardiac surgery increases the risk of in-hospital mortality by 11.8 times.

Gastrointestinal complications are very diverse and can threaten the patient after surgery with different symptoms. In some patients, more than one GIC may develop together, and these conditions may cause higher mortality rates than a single GIC.^[46,47] The incidence of GICs after cardiac surgery varies between studies. The difference, we believe, is in how the studies describe complications. While some studies have concentrated on GICs only that may necessitate surgery, such as acute mesenteric ischemia or GI bleeding, others have broadened the definition of GICs by screening for hyperbilirubinemia, pseudomembranous hyperamylasemia, and enterocolitis. Mangi et al.^[48] reported an inverse relationship between the incidence of GICs and reported mortality due to GICs. There is no controversy regarding the acceptance of mesenteric ischemia as the most fatal GIC.^[3,7,8,17,19,20,29] On the contrary, discussions about the most common GICs continue for the aforementioned reasons. In recent studies by

Hess et al.^[5] and Haywood et al.,^[23] the most common GIC was *Clostridium difficile* infection diagnosed by polymerase chain reaction (PCR) test. Haywood et al.^[23] also diagnosed *Clostridium difficile* infection by PCR test. A few studies have reported that hyperbilirubinemia is the most common GICs.^[1] On the other hand, overall, most studies have reported that GI bleeding is the most common GIC after cardiac surgery.^[2,3,7-9,14,19,29]

In healthy individuals, the GI organs require 20% of cardiac output.^[31] A significant decrease in the mesenteric blood flow is the main culprit for GICs. Peri- and postoperative hypotension, low cardiac output syndrome, high peep due to prolonged ventilation, embolization to the celiac, superior mesenteric, and inferior mesenteric arteries all reduce the splanchnic blood flow.^[49,50] Splanchnic blood flow reduction not only results in mesenteric ischemia, but also causes other GICs such as GI bleeding, pancreatitis, and cholecystitis that develop with ischemic mucosal injury. In the meta-analysis, we found that peripheral artery disease was 2.4 times more frequent in patients with GICs. Extensive atherosclerosis in patients with PVD may complicate maintaining the splanchnic blood flow.

There are many pre-, intra-, and postoperative risk factors that facilitate the development of GICs in cardiac surgery. In this meta-analysis, we found that the CPB time of patients with GICs was significantly longer than that of patients without GICs. It has been reported that inflammatory mediators released due to CPB cause ischemia-reperfusion injury, increase acidosis in the gastric mucosa, and lead to impaired mucosal integrity.^[51-53] Moreover, microembolism, hypothermia, and rewarming may cause deterioration in splanchnic perfusion.^[1,53,54] Interestingly, studies comparing the development of GICs between off-pump and on-pump cardiac surgery have found no significant difference between the two techniques in the development of GICs.^[55,56] Fiore et al.^[57] showed that the splanchnic blood flow was significantly reduced, when the heart was verticalized during off-pump surgery. In the perioperative period of off-pump surgery, mesenteric hypoperfusion and the need for inotrope and vasopressor may cause GICs. On the other hand, there was no significant difference between patients with and without GICs in terms of prolonged ACC time, which has historically been associated with adverse outcomes following cardiac surgery. This result can be explained by the relatively short ACC times of the studies included in the meta-analysis.

Acute renal failure results from hypoperfusion, such as GICs after cardiac surgery. These two distinct clinical conditions with similar pathogenesis can frequently coexist. The meta-analysis showed that patients with GICs developed ARF 11.3 times more often than patients without GICs. In addition, ARF facilitates the development of GICs by decreasing the colonic transit time.^[58]

This meta-analysis has some limitations. First, the heterogeneity scores in the meta-analysis are high. A possible cause of heterogeneity is the difference in design between studies. There is no clear consensus on the definition of GIS developed after cardiac surgery. Therefore, there are significant design differences between studies. Second, in this meta-analysis, it cannot be concluded that postoperative outcomes such as ARF, sepsis, and myocardial infarction are the cause or consequence of GICs. Third, all types of cardiac surgery were included in the meta-analysis, and subgroup analyses such as isolated coronary artery bypass grafting or isolated valve surgery were unable to be performed. This meta-analysis was carried out to analyze current data and draw conclusions for clinicians and future studies.

In conclusion, gastrointestinal complications usually occur in elderly patients with a higher incidence of preoperative comorbidities. Moreover, the diagnosis of gastrointestinal complications is often a clinical challenge, and symptoms may be overshadowed by sedation and severe cardiac and pulmonary conditions. Delayed diagnosis of gastrointestinal complications can be often associated with catastrophic outcomes. Acute renal failure, new-onset atrial fibrillation, myocardial infarction, strokes, and sepsis are widespread in patients with gastrointestinal complications after cardiac surgery. Based on available data, the development of gastrointestinal complications increases the hospital mortality rate by 11.8 times.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: Z.M.D.; Design: Z.M.D., M.B., M.C.K.; Control/supervision, critical review: T.A.; Data collection and/or processing: Z.M.D., B.T., M.C.K.; Analysis and/or interpretation: Z.M.D., B.T.; Literature review, references and fundings: Z.M.D., M.B., B.T., M.C.K., T.A.; Writing the article: Z.M.D., M.B.

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