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Professors Monjur Ahmed and Florin Burada

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Dear Professors Ahmed and Burada,

Thank you for your review and consideration of the paper *'The effect of obesity on post-operative outcomes following colorectal cancer surgery'*

We thank both yourselves and the peer reviewers for their feedback and kind comments and recommendations of the paper. These have been very helpful in strengthening the paper.

We have addressed each point from the peer review process below. A revised version of the manuscript incorporating the suggested changes is enclosed.

Kind regards,

Dr Derek Mao (on behalf of all authors)

Reviewer 1

“Different RACES may not represent the postoperative complications of colorectal cancer patients, suggesting that future design prospective controlled multicenter research has more guidance value. In addition, body mass index (BMI) is based on an individual's height and weight, which cannot reflect particular body mass contents such as muscle mass.”

Thank you for your comment. Although body mass index (BMI) has been accepted in the literature as a reliable surrogate marker of obesity (4) and is the universal definition of obesity as per the World Health Organisation (5), there are some limitations.

As you have mentioned, some of these shortcomings is that BMI is distributed differently in different races and that it does not directly reflect particular body mass contents (for example, muscle vs adipose). We recognised the limitations of BMI in our discussion in the original submission as follows: *“We recognise that as an anthropometric measure, BMI has its limitations in the ability to identify visceral obesity, and also is distributed differently among ethnic groups (26)”*

As a research group, we discussed at length the reasons to use BMI as a marker of obesity rather than more specific measures of intra-abdominal fat such as visceral fat area (VFA).

Firstly, the majority of studies available use BMI to define obesity, so we were able to compare our results directly against different institutions which we have cited in our discussion.

Secondly, BMI has been accepted to be indicative of whole-body fat, allowing for the analysis of adipose-associated pathophysiological processes (19). This is certainly true in our data, as we have shown that the BMI ≥30 (obese) group have statistically significant higher rates of adipose-associated co-morbidities such as hypertension, obstructive sleep apnoea, and type II diabetes. A large advantage of our study is its ability to capture very specific co-morbidity information such as those mentioned above, which very few papers discussing the effect of elevated BMI on colorectal cancer surgery outcomes have been able to do. The fact that our BMI ≥30 (obese) group have significantly higher rates of adipose-associated diseases has reassured us that using BMI as a surrogate marker has allowed us to capture the right patients with our outcome of interest, being increased visceral adiposity.

“More and more studies have confirmed that lean body weight, body fat percentage, and some nutritional indicators strongly correlated with tumors' occurrence, development, and prognosis. It is suggested to include body composition analysis, NRS-2002, PG-SGA, and nutritional prognostic indicators”

We strongly agree with you that body composition is associated with tumour biology, development and prognosis in colorectal cancer. The indicators that you have stated such as the NRS-2002 and PG-SGA are primarily used for assessing risk factors for malnutrition.

Although the impact of malnutrition on colorectal cancer outcomes are important, these are separate issues to our topic which is specifically focussed on obesity and intra-abdominal adiposity.

Nonetheless, an in-depth analysis of assessing the impact of malnutrition and/or lean body mass on colorectal cancer surgery outcomes is certainly an interesting avenue of research we can explore in a future study. We have stated that this is a further area of research in the ‘article highlights’ (research perspectives) section of the paper as follows: *“In addition, the effect of nutritional status and body composition on post-operative outcomes can be explored.”*

Reviewer 2

“It would be useful a more detailed presentation of postoperative complications pulling apart right colon, left colon and rectum; and doing the same by type of surgical procedure.”

We thank you for your comment and strongly agree that this is a valuable piece of information. As per your recommendation, we have presented a detailed comparison in the subgroups of patients with right sided colon cancer (caecum to transverse colon), left sided colon cancer (splenic flexure to sigmoid colon) and rectal cancer.

Similar to the findings in the overall cohort, there were no differences between obese and non-obese patients in the incidence of a post-operative complication, high-grade complication, surgical complication, or medical complication in any of the three subgroups.

This strengthens our primary finding that post-operative outcomes in obese patients are equivalent to non-obese patients. It is reassuring to see that is not influenced by cancer location.

The type of colorectal surgical procedures undertaken are primarily determined from the location of the cancer, so we have addressed this point by pulling apart patients into subgroups based off cancer location as above.

The changes have been incorporated into the paper as follows:

Materials and methods: *Furthermore, post-operative outcomes of obese versus non-obese patients were compared in subgroups divided by cancer location. Patients were divided into a right sided colon cancer (caecum to transverse colon) subgroup (table 5), left sided colon cancer (splenic flexure to sigmoid colon) subgroup (table 6) and a rectal cancer subgroup (table 7).*

Results: *Obese and non-obese patients in the right sided colon cancer subgroup had equivalent outcomes, with no differences in the incidence of post-operative complications (52.2% vs 54.1%, p = 0.61), high-grade complications (17.4% vs 15.6%, p = 0.73), surgical complications (23.9% vs 25.4%, p = 0.88), or medical complications (27.2% vs 26.8%, p = 1.00).*

Similarly in the left sided colon cancer subgroup there were no differences between obese and non-obese patients in the percentage of post-operative complications (47.5% vs 37.1%, p = 0.09), high grade complications (18.0% vs 9.8%, p = 0.11), surgical complications (27.9% vs 20.3%, p = 0.27), or medical complications (9.8% vs 19.6%, p = 0.10).

In the rectal cancer subgroup, there were also no differences between obese and non-obese patients in the prevalence of post-operative complications (70.0% vs 54.2%, p = 0.68), high-grade complications (35.0% vs 31.2%, p = 0.78), surgical complications (35.0% vs 37.5%, p = 1.00), or medical complications (25.0% vs 27.1%, p = 1.00).

Tables:

Table 5 –post-operative outcomes in the subgroup of patients with right sided colon cancer

		BMI <30 (% of group)	BMI ≥30 (% of group)	Total	P Value
Patients		205	92	297	
	No complication	94 (45.9)	44 (47.8)	138	0.61
	Complication	111 (54.1)	48 (52.2)	159	
	I	21 (10.2)	9 (9.8)	30	
	II	58 (28.3)	23 (25.0)	81	
Post-operative complication (CD grade)	IIIa	19 (9.3)	7 (7.6)	26	
	IIIb	3 (1.5)	1 (1.1)	4	
	IVa	8 (3.9)	5 (5.4)	13	
	IVb	0 (0.0)	2 (2.2)	2	
	V	2 (1.0)	1 (1.1)	3	
	No complication or low-grade complication (CD I-II)	173 (84.4)	76 (82.6)	249	0.73
	High-grade complication (CD IIIa-V)	32 (15.6)	16 (17.4)	48	
Any surgical complication		52 (25.4)	22 (23.9)	74	0.88
Specified surgical complications	Abdomino-pelvic collection	7 (3.4)	3 (0.0)	10	0.10
	Anastomotic leak	7 (3.4)	0 (0.0)	7	1.00
	Wound infection	10 (4.9)	3 (3.3)	13	0.76
	Prolonged ileus	26 (12.7)	14 (15.2)	40	0.58
	Post-operative haemorrhage	1 (0.5)	2 (2.2)	3	0.23
	Return to theatre	3 (1.5)	1 (1.1)	4	1.00
	Post-operative sepsis	2 (1.0)	1 (1.1)	3	1.00
Any medical complication		55 (26.8)	25 (27.2)	80	1.00
Specified medical complications	VTE (DVT/PE)	2 (1.0)	1 (1.1)	3	1.00
	Pneumonia	14 (6.8)	6 (6.5)	20	1.00
	Ischaemic cardiac event	2 (1.0)	3 (3.3)	5	0.17
	Cardiac arrhythmia	20 (9.8)	6 (6.5)	26	0.51
	Respiratory failure	4 (2.0)	5 (5.4)	9	0.14
	Renal failure	7 (3.4)	6 (6.5)	13	0.23
	Unplanned ICU admission	8 (3.9)	4 (4.3)	12	1.00
Post-operative length of stay (days)		7 (IQR 5-11)	6 (IQR 5-11)		0.91

BMI, body mass index; CD, Clavien-Dindo; VTE, venous thrombo-embolism, DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 6 –post-operative outcomes in the subgroup of patients with left sided colon cancer

		BMI <30 (% of group)	BMI ≥30 (% of group)	Total	P Value
Patients		143	61	204	
	No complication	90 (62.9)	32 (52.5)	122	0.09
	Complication	53 (37.1)	29 (47.5)	82	
	I	7 (4.9)	6 (9.8)	13	
	II	32 (22.4)	12 (19.7)	44	
Post-operative complication (CD grade)	IIIa	3 (2.1)	6 (9.8)	9	
	IIIb	5 (3.5)	2 (3.3)	7	
	IVa	3 (2.1)	2 (3.3)	5	
	IVb	0 (0.0)	1 (1.6)	1	
	V	3 (2.1)	0 (0.0)	3	
	No complication or low-grade complication (CD I-II)	129 (90.2)	50 (82.0)	179	0.11
	High-grade complication (CD IIIa-V)	14 (9.8)	11 (18.0)	25	
Any surgical complication		29 (20.3)	17 (27.9)	46	0.27
Specified surgical complications	Abdomino-pelvic collection	7 (4.9)	2 (3.3)	9	0.73
	Anastomotic leak	4 (2.8)	2 (3.3)	6	1.00
	Wound infection	4 (2.8)	3 (4.9)	7	0.43
	Prolonged ileus	17 (11.9)	9 (14.8)	26	0.65
	Post-operative haemorrhage	1 (0.7)	0 (0.0)	1	1.00
	Return to theatre	5 (3.5)	3 (4.9)	8	0.70
	Post-operative sepsis	3 (2.1)	0 (0.0)	3	0.56
Any medical complication		28 (19.6)	6 (9.8)	34	0.10
Specified medical complications	VTE (DVT/PE)	1 (0.7)	1 (1.6)	2	0.51
	Pneumonia	5 (3.5)	2 (3.3)	7	1.00
	Ischaemic cardiac event	1 (0.7)	0 (0.0)	1	1.00
	Cardiac arrhythmia	6 (4.2)	0 (0.0)	6	1.00
	Respiratory failure	4 (2.8)	2 (3.3)	6	1.00
	Renal failure	4 (2.8)	0 (0.0)	4	0.32
	Unplanned ICU admission	5 (3.5)	2 (3.3)	7	1.00
Post-operative length of stay (days)		7 (IQR 5-10)	7 (IQR 5-10)		0.89

BMI, body mass index; CD, Clavien-Dindo; VTE, venous thrombo-embolism, DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 7 –post-operative outcomes in the subgroup of patients with rectal cancer

		BMI <30 (% of group)	BMI ≥30 (% of group)	Total	P Value
Patients		48	20	68	
Post-operative complication (CD grade)	No complication	22 (45.8)	6 (30.0)	28	0.68
	Complication	26 (54.2)	14 (70.0)	40	
	I	3 (6.3)	2 (10.0)	5	
	II	8 (16.7)	5 (25.0)	13	
	IIIa	5 (10.4)	2 (10.0)	7	
	IIIb	5 (10.4)	3 (15.0)	8	
	IVa	2 (4.2)	2 (10.0)	4	
	IVb	0 (0.0)	0 (0.0)	0	
	V	3 (6.3)	0 (0.0)	3	
	No complication or low-grade complication (CD I-II)	33 (68.8)	13 (65.0)	46	0.78
	High-grade complication (CD IIIa-V)	15 (31.2)	7 (35.0)	22	
Any surgical complication		18 (37.5)	7 (35.0)	25	1.00
Specified surgical complications	Abdomino-pelvic collection	2 (4.2)	1 (5.0)	3	1.00
	Anastomotic leak	1 (2.1)	2 (10.0)	3	0.20
	Wound infection	5 (10.4)	0 (0.0)	5	0.31
	Prolonged ileus	6 (12.5)	3 (15.0)	9	1.00
	Post-operative haemorrhage	1 (2.1)	0 (0.0)	1	1.00
	Return to theatre	5 (10.4)	3 (15.0)	8	0.68
	Post-operative sepsis	1 (2.1)	0 (0.0)	1	1.00
Any medical complication		13 (27.1)	5 (25.0)	18	1.00
Specified medical complications	VTE (DVT/PE)	1 (2.1)	0 (0.0)	1	1.00
	Pneumonia	0 (0.0)	0 (0.0)	0	
	Ischaemic cardiac event	2 (4.2)	2 (10.0)	4	0.58
	Cardiac arrhythmia	4 (8.3)	2 (10.0)	6	1.00
	Respiratory failure	2 (4.2)	1 (5.0)	3	1.00
	Renal failure	1 (2.1)	1 (5.0)	2	0.50
	Unplanned ICU admission	3 (6.3)	0 (0.0)	3	0.55
Post-operative length of stay (days)		9 (IQR 6-14)	10 (IQR 5-21)		0.91

BMI, body mass index; CD, Clavien-Dindo; VTE, venous thrombo-embolism, DVT, deep vein thrombosis; PE, pulmonary embolism.

Science Editor

“This retrospective study that mainly evaluated the effect of obesity on postoperative colorectal cancer patients. It is a summary of the 10-year experience of a single center and has certain clinical guiding significance. The recommendations made by the first reviewer will help to improve the significance of the article’s evidence-based medicine and to differentiate the obese population more finely.”

Thank you for your comments. The comments and recommendations made by the reviewers have been very insightful and helpful in strengthening the paper. The points raised have been responded to, with appropriate changes included in the resubmitted revision.

Company Editor-In-Chief

"…Before final acceptance, authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content."

Thank you for your comment. As per your instructions we have changed our tables to only have a top line, bottom line and column line with other table lines hidden.