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Humanistic Burden of Cachexia in Gastrointestinal Cancers: A Systematic Literature Review

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1 BACKGROUND

- Cancer cachexia is characterized by progressive muscle loss that is not fully reversible with nutritional support.[1]
- Upper GI and pancreatic cancers are particularly susceptible because of reduced intake, obstruction, treatment toxicity, and malabsorption[2]; however, cachexia-related patient burden remains inconsistently characterized.
- This AI-enabled SLR assessed the humanistic burden of cachexia across GI cancers, including Health-related Quality of Life (HRQoL), symptoms, functioning, Activities of Daily Living (ADL), physical function, performance status, and caregiver burden.

2 METHODS

- This SLR was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement. MEDLINE and Embase (2015-2025), conference proceedings (2021-2025), and grey literature were searched for relevant English-language publications in December 2025.
- Eligible publications included SLRs and observational studies providing data on humanistic outcomes in GI cancer patients with cachexia; where GI cancer-specific data were sparse or unavailable (e.g., ADL and caregiver burden), evidence from broader overall cancer populations, particularly high-quality SLRs, was included.
- AI supported title/abstract (ti/ab) screening, full-text screening, and data extraction, with one or more of the models (BiomedVLP-CXR-BERT, OpenAI o3-mini/o4-mini, and Gemini 2.5 Pro) selected for each stage. All AI-included records at ti/ab screening and FTS were verified by reviewers, and all extracted data underwent 100% QC against source PDFs.
- Quality assessment conducted using the NOS for cohort studies, an adapted NOS for cross-sectional studies, and AMSTAR for SLRs.

3 RESULTS

Study and patient characteristics

- Of 5,792 retrieved citations, FTS identified 115 GI cancer-specific publications, of which 27 (25 primary studies) reported humanistic burden data. Of 211 included non-GI cancer publications, four (2 primary studies and 2 SLRs) were included to inform evidence gaps.
- GI cancer sample sizes ranged from 56 to 10,568 (with vs. w/o cachexia: 22–3,906 vs. 25–6,662); mainly involving older patients with advanced or mixed GI cancers; most studies were conducted in China and Japan.
- The median study quality was 7/9 for NOS and 7.5/11 for AMSTAR.
- No GI cancer-specific studies on caregiver burden were identified, hence results from 2 SLRs in overall cancer are summarized.

HRQoL

- *HRQoL* was *consistently poorer with cachexia* across most studies and cachexia definitions (Table 1).
- EORTC QLQ-C30 summary, global health, and global QoL scores were generally lower in patients with versus without cachexia.
- Overall HRQoL declined progressively with increasing cachexia severity/stage.[3-8]

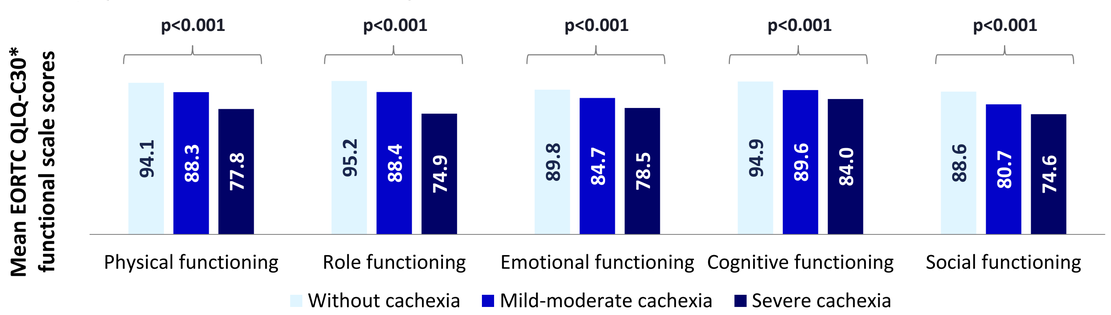
Table 1. HRQoL (EORTC QLQ-C30^ scores) in GI cancer patients by cachexia status and severity/ stage

Score type	GI cancer site	Cachexia criteria	Average score (with vs. w/o cachexia, unless specified otherwise)
Summary	GC[3]	AWGC	79.5 vs. 92.3#,†
	GC[4]	Fearon	87.2 vs. 90.3#,†
	Mixed GI[5]	CCSI	Mild-moderate vs. severe vs. w/o cachexia: 86.0 vs. 79.1 vs. 92.5*,†
Overall/ global health status	GC[3]	AWGC	50.0 vs. 83.3#,†
	Mixed GI[6]	Fearon	66.7 vs. 66.7*; p=NR
	PDAC[7]	Vigano criteria	Pre-cachexia vs. cachexia vs. refractory vs. w/o cachexia: 60.5 vs. 51.4 vs. 27.1 vs. 65.7*; p=NR
Overall/ global QoL	GC[4]	Fearon	58.3 vs. 66.7#,†
	GC[8]	Fearon	65.6 vs. 71.0*,†
	GC[8]	AWGC	66.6 vs. 71.0*,†
	Mixed GI[5]	CCSI	Mild-moderate vs. severe vs. w/o cachexia: 67.7 vs. 51.7 vs. 78.8*,†
	PDAC[7]	Vigano criteria	Pre-cachexia vs. cachexia vs. refractory vs. w/o cachexia: 68.8 vs. 54.8 vs. 34.1 vs. 71.5*; p=NR

*Mean score; #Median score; †p<0.05; ^**EORTC QLQ-C30** summary score range 0-100; higher scores indicate better QoL
Note: Scores for overall/global health status and overall/global QoL are presented as reported in the publications, with one study[7] reporting both as separate items

- Gastric cancer patients with cachexia had ~*6-fold higher odds of poor HRQoL* (<median EORTC QLQ-C30 summary score) after adjustment for clinical and nutritional factors (OR 5.92; 95% CI 3.27–10.73; p<0.001).[3]
- EORTC QLQ-C30 *functional outcomes were mixed* across studies, although functioning worsened progressively with increasing cachexia severity in one mixed GI cancer study (Fig. 1). [3-6,8,10]

Figure 1. Mean HRQoL functional scale scores (EORTC QLQ-C30*) in pre-operative mixed GI cancer patients, by cachexia status and severity^[5]



*EORTC QLQ-C30 functional scale score range 0-100; higher scores indicate better functioning; ^Based on CCSI which incorporates weight loss, inflammation, prealbumin, appetite, and physical status; scores <9, 9–18, and ≥19 indicate no, mild–moderate, and severe cachexia, respectively.

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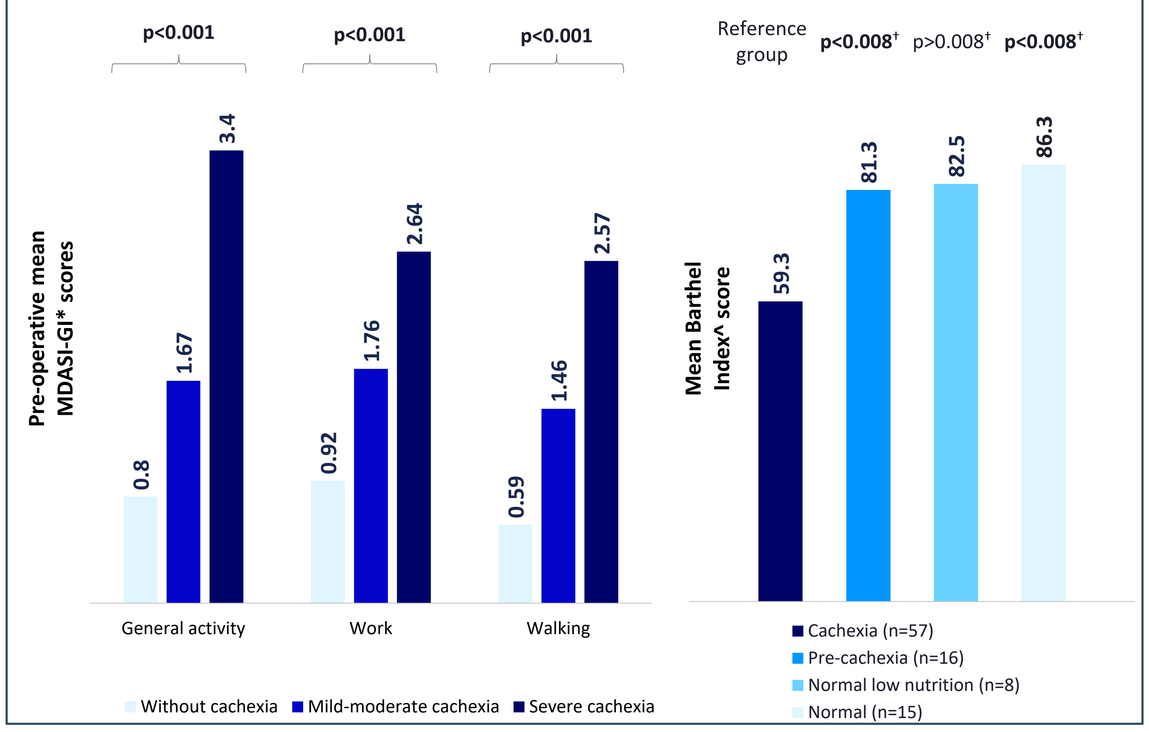
HRQoL (continued)

- Cachexia was generally associated with *greater symptom burden* across GI cancers.
  - **EORTC QLQ-C30**: greater fatigue and appetite loss with cachexia.[3-5,8,10]
  - **EORTC QLQ-CAX24**: greater food aversion, eating/weight-loss worry, loss of control, and dry mouth in rectal cancer.[11]
  - **EORTC QLQ-PAN26**: PDAC symptoms worsened progressively with advancing cachexia stage.[7]

ADL/functioning

- Cachexia was generally associated with *poorer ADL and greater functional dependence*, with worsening interference in general activity, work, and walking as cachexia severity increased (Fig. 2a and 2b); evidence was limited and not fully consistent across studies.[5,9,13,14]

Figure 2 (a) Interference of GI cancer-related symptoms on patients' pre-operative activity in past 24 hours, by cachexia severity[5]; Figure 2 (b) Functioning at the start of rehabilitation, by cachexia/nutritional status (groups defined by mGPS)[9]



***MDASI-GI** score range: 0-10; higher scores indicate greater symptom interference; **^Barthel Index:** score range: 0 to 100; higher score indicates greater functional independence; †Bonferroni-adjusted significance threshold α = 0.008 for comparison of each sub-group with the cachexia group

Physical function and performance status

- Cachexia was associated *with poorer physical function and performance status* across GI cancers.
  - HGS was significantly lower in those with vs. without cachexia (21.5–28.8 vs 26.0–33.1 kg);[3-5,8,15,16] Sex-stratified data from two studies showed lower HGS with cachexia in both males (8.3–29.2 vs 19.6–34.9 kg) and females (2.3–18.0 vs 18.9–22.4 kg).[12, 17]
  - 6MWD was significantly shorter in patients with cachexia (470 vs 505 m)[12], with a between-group difference of 35 m that exceeded the MCID threshold (14–30.5 m)[18], suggesting a potentially clinically meaningful difference.
  - HGS, 6MWD, SPPB, and self-reported function *declined with increasing cachexia severity*.[5,17]
  - Poor performance status was more frequent with cachexia (ECOG PS ≥2: 0–51.7% vs 0–33.9%).[3,4,8,12,19-24]

Caregiver burden (overall cancer)

- Caregivers of patients with cancer cachexia experienced *substantial practical, emotional, and social burden*.[25,26]
- Burden included disrupted daily life, eating-related conflict, stress, helplessness, and social isolation.
- Caregivers also reported insufficient support from healthcare professionals.

4 LIMITATIONS

- Restriction to English-language publications, substantial methodological and clinical heterogeneity precluding meta-analysis, predominance of small retrospective/single-center studies with limited confounder adjustment, and geographic concentration in a few countries (China and Japan).

5 CONCLUSIONS

- Cachexia is associated with substantially worse HRQoL, symptoms, and physical activity in GI cancer, supporting earlier recognition and management.
- Limited evidence on functioning, and lack of data on physical activity, and GI-specific caregiver data highlight key unmet needs.

References:

[1]Fearon et al, 2011. Lancet Oncol. 12(5):489-95; [2]Brown et al, 2022. Curr Treat Options Oncol. 23(12):1732-1747; [3]Huang et al, 2025b. Front Nutr. 12:1659669; [4]Zhang et al, 2025. J Cachexia Sarcopenia Muscle. 16(3):e13859; [5]Wang et al, 2023. Nutrition. 114:112114; [6]Medeiros et al, 2024. Radiol Bras. 2:57:e20240012; [7]Permuth et al, 2024. Front Oncol. 14:1362244; [8]Zhang et al, 2024. Clin Nutr. 43(6):1524-1531; [9]Akezaki et al, 2020. J Phys Ther Sci. 32(1):16-19; [10]Huang et al, 2025a. BMC Cancer. 9;25(1):1293; [11]Cintoni et al, 2024. Nutrients. 16(24):4277; [12]Fugane et al, 2025. Clin Nutr. 47:112-118; [13]Nordan et al, 2024. Am Surg. 90(4):585–591; [14]Furuse et al, 2024. Int J Clin Oncol. 29(4):456–463; [15]Wang et al, 2024. Eur J Surg Oncol. 50(10):108580; [16]Chen et al, 2019. Cancer Manag Res. 11:8101-8110; [17]Ozorio et al, 2017. Nutr Cancer. 69(5):772-779; [18]Bohannon and Crouch, 2017. J Eval Clin Pract. 23(2):377–381; [19]Brown et al, 2025. Cancers (Basel). 17(3):448; [20]Fukuta et al, 2019. Nutrition. 58:65-68; [21]Fukahori et al, 2021. Support Care Cancer. 29(1):341-348; [22]Ruan et al, 2023. J Cachexia Sarcopenia Muscle. 14(6):2813-2823; [23]Okada et al, 2024. Ann Oncol. 35:S1600; [24]Takeda et al, 2021. Int J Clin Oncol. 26(7):1293-1303; [25]Cooper et al, 2015. J Cachexia Sarcopenia Muscle. 6(1):99–111; [26]Wheelwright et al, 2016. Palliat Med. 30(2):149–160.

Abbreviations:

6MWD = 6-minute walk distance; AI = artificial intelligence; ADL = activities of daily living; AMSTAR = A MeaSurement Tool to Assess Systematic Reviews; AWGC = Asian Working Group for Cachexia; CCSI = Cancer Cachexia Staging Index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CAX24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer Cachexia 24; EORTC QLQ-PAN26 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic Cancer 26; FTS = full-text screening; GC = gastric cancer; GI = gastrointestinal; HRQoL = health-related quality of life; HGS = hand grip strength; MCID = Minimal Clinically Important Difference; MDASI-GI = MD Anderson Symptom Inventory Gastrointestinal Cancer Module; mGPS = Miki's modified Glasgow Prognostic Score; NOS = Newcastle-Ottawa Scale; NR = not reported; OR = odds ratio; PDAC = pancreatic ductal adenocarcinoma; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL = quality of life; SLR = systematic literature review; SPPB = Short Physical Performance Battery; ti/ab = title/abstract; w/o = without

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