

A Systematic Literature Review of Health-Related Quality of Life of Patients with Advanced Esophageal Cancer

PCR67

Shruti Nambiar¹, Ilia Ferrusi¹, Kavita Rodha², Manik Kalra³, Elizabeth Smyth⁴

¹Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; ²Novartis Ireland Limited, Dublin, Ireland; ³Novartis Healthcare Pvt Ltd, Hyderabad, India; ⁴Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Background

- Worldwide, esophageal squamous cell carcinoma (ESCC) is the most prevalent type of esophageal cancer (EC), accounting for 90% of all cases^{1,2}
- Patients with advanced EC experience reduced quality of life (QoL) because of progressive dysphagia, painful swallowing, dyspepsia, heartburn, and malnutrition³
- These clinical features in advanced stage are extremely aggressive and are associated with high disease-related mortality³
- A 5-year survival of 3% among Stage IV EC patients reflects poor prognosis and places significant burden on patients' lives⁴
- In recent years, immune checkpoint inhibitors have emerged as a promising treatment option. However, median survival of Stage IV disease remains <1 year^{6,6,7,8,9,10}

Objective

- A systematic literature review (SLR) was conducted to characterize the humanistic burden of ESCC using health-related quality of life (HRQoL) outcomes and health utilities in advanced/metastatic EC patients and to evaluate the related gaps in published literature

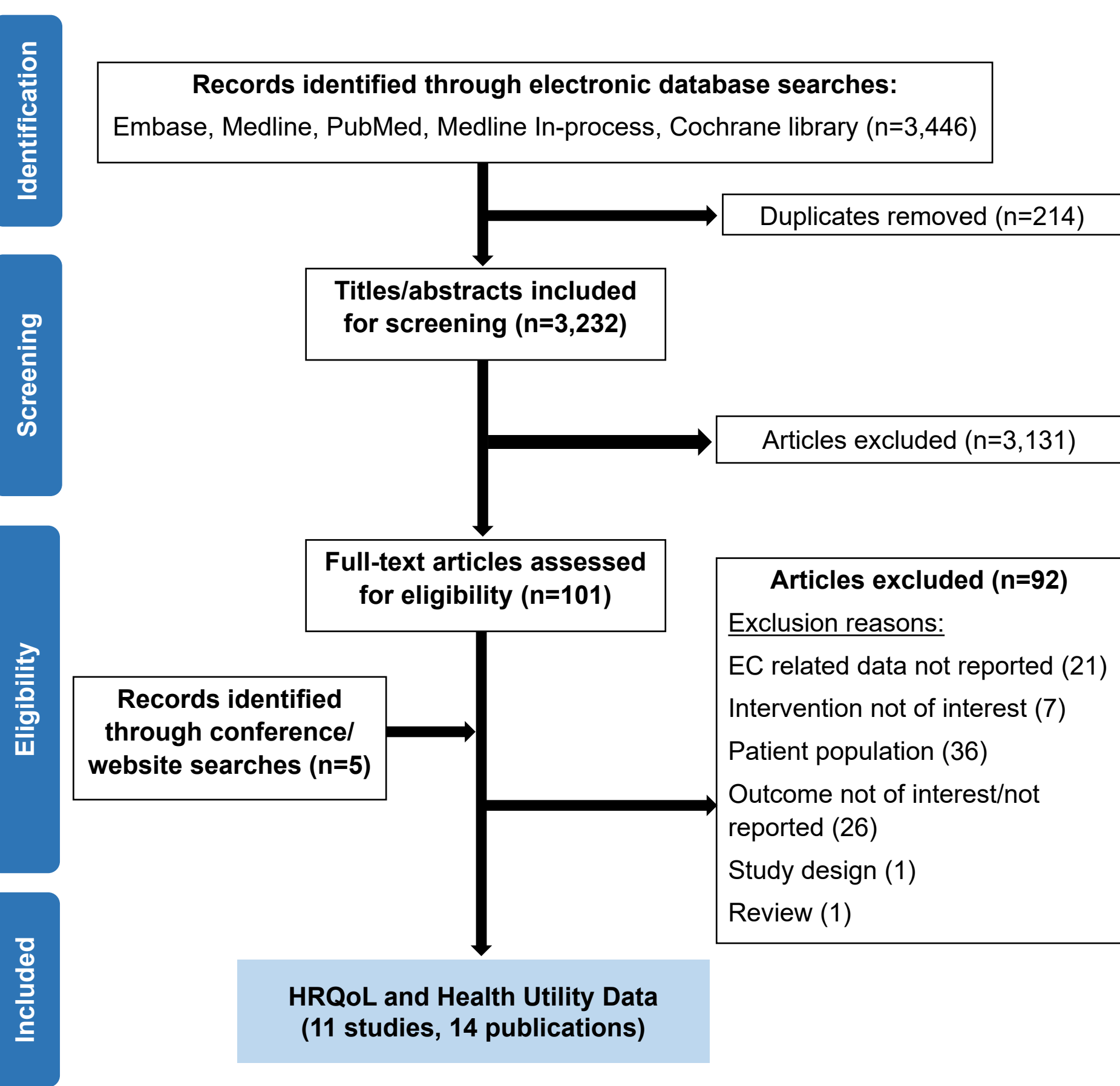
Methods

- A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹ The design and implementation were guided by PICOS (Population, Intervention, Comparison, Outcomes and Study type) criteria
- Study eligibility criteria were as follows:
 - Population: Adult patients (≥18 years) irrespective of race or gender; with advanced unresectable or metastatic EC (inclusive of 1L/2L patients)
 - Interventions/Comparators: Systemic therapies (chemotherapy agents, immunotherapy agents)
 - Outcomes: Health utilities, Patient-reported outcomes (PROs), HRQoL outcomes
 - Study Designs: Randomized controlled trials (RCTs), economic evaluations, observational studies reported in English language
- Embase, PubMed, and Cochrane library were searched from inception to August 2021, complemented by conference searches from 2019-2021 to identify English-language publications reporting the humanistic burden of advanced/metastatic EC
- Screening and data extraction were performed by two independent researchers, with any differences in results reconciled by a third reviewer

Results

- Overall, 3446 publications were screened and finally, 11 studies (14 publications) met the criteria for inclusion reporting HRQoL or health utilities data in advanced unresectable or metastatic EC patients (Figure 1)
- Included studies were conducted across USA (3), Canada (1), China (4), UK (1), and multinational settings (2)

Figure 1. PRISMA Diagram for Systematic Literature Review



HRQoL Outcomes

- HRQoL outcomes were reported in 6 studies (8 publications), of which 3 were observational studies and 3 were RCTs
- Across various PRO instruments, there is demonstrable humanistic burden of EC in advanced stages compared to healthy individuals (Table 1)
- Burden increases as the disease stage worsens in terms of general health as well as symptom-specific burden (Table 1)
- HRQoL was reported using different PRO measures across RCTs and were only reported in RCTs comparing immuno-oncology (IO) agents vs chemotherapy
- Generic (EuroQoL 5-dimension [EQ-5D]) and cancer-specific (European Organization for the Research and Treatment of Cancer [EORTC] core and symptom modules) scales were utilized to measure HRQoL
- Across 3 RCTs, patients on IO agents typically reported improvement in general health scores i.e., EQ-5D scores and lower risk of deterioration in EORTC core and symptom-specific scales vs chemotherapy (Table 2)

Table 1 HRQoL Burden of Advanced, Stage IV Esophageal Cancer Reported Across Observational Studies

PRO Study, Location	Assessment Outcomes
General Health Measures	
EQ-5D VAS Liu 2018 ¹² , China	Significantly lower EQ-5D VAS score in EC patients vs controls (62.17 vs 85.14, P<0.001)
EQ-5D Liu 2018 ¹² , China	46.1% patients reported problems in mobility; 41.2% in self-care; 45.6% in usual activities; 63.2% in pain/discomfort; and 48.8% in anxiety/depression
EQ-5D HUS Liu 2018 ¹² , China Doherty 2018 ¹³ , Canada	Significant impact on health utility scores in Stage IV EC patients vs healthy controls (0.66 vs 0.96, P<0.001) Lower health utility scores in Stage IV/recurrent EC patients (0.72) vs Stage II/III EC patients (0.82)
Cancer Specific Measures	
FACT-E & FACT-G Doherty 2018 ¹³ , Canada	Scores on FACT-E and FACT-G indicate impairment in HRQoL in EC patients (112.8 and 72.5, respectively) Palliative chemotherapy did not result in significant improvement in these patients (FACT-E score = 122.5, P=0.14 and FACT-G score = 72.1, P=0.87)
LASA scale Sio 2013 ¹⁴ , US	Metastatic patients had worst QoL in 11 out of 12 domains in comparison to early EC patients
PR-ECOG Doherty 2018 ¹³ , Canada	Lower scores observed in Stage IV/recurrent EC patients in comparison to Stage II/III EC patients
Symptom Burden Measures	
Symptom complex summary scores (pain, dysphagia, nausea, dyspnea, loss of appetite, fatigue) Doherty 2018 ¹³ , Canada	Scores were lower in Stage IV/recurrent EC patients in comparison to Stage II/III EC patients indicating significantly impaired QoL in Stage IV patients

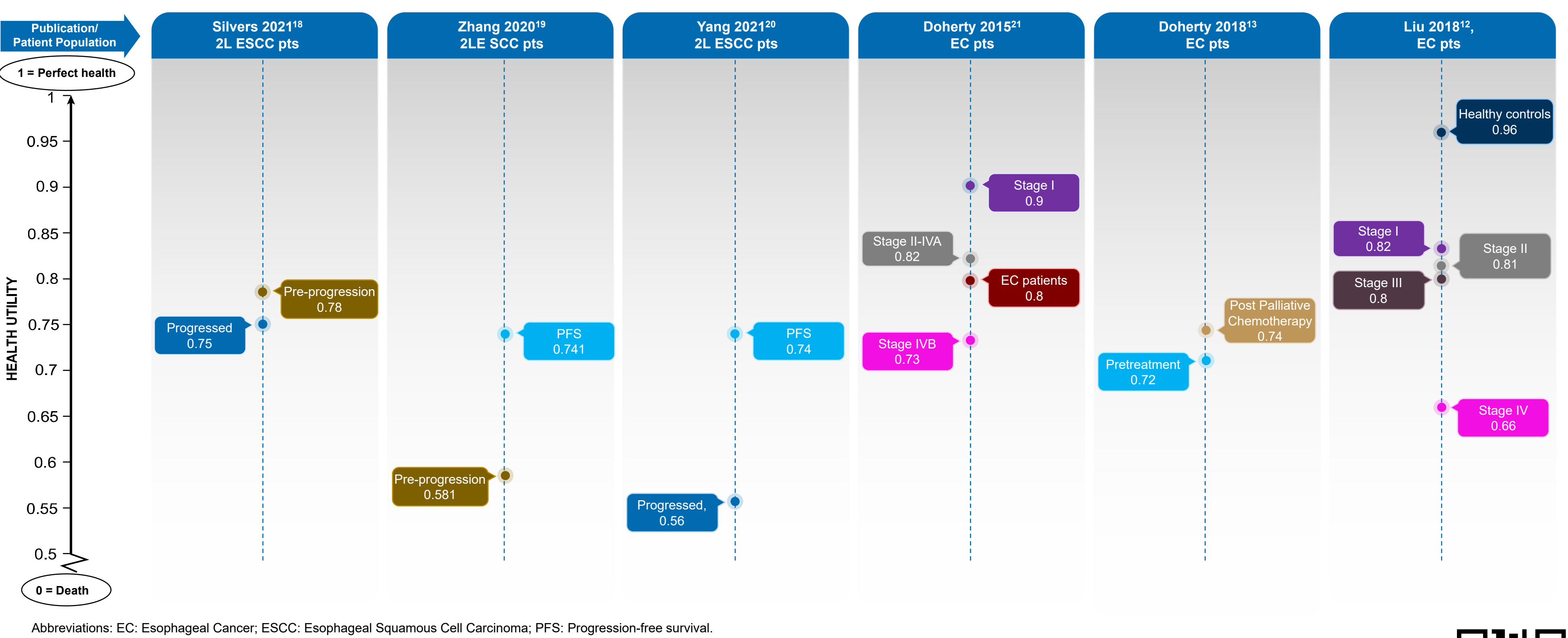
Indicates negative impact on HRQoL
Abbreviations: EC: Esophageal Cancer; EQ-5D: EuroQoL 5-dimension questionnaire; EQ-5D VAS: EuroQoL 5-dimension Visual Analogue Scale; HRQoL: Health-related quality of life; HUS: Health utility scores; FACT-E: Functional Assessment of Cancer Therapy – Esophageal; FACT-G: Functional Assessment of Cancer Therapy – General; LASA: Linear Analog Self-Assessment; PR-ECOG: Patient-reported Eastern Co-operative Oncology Group scale

Table 2 Overview of HRQoL Assessment from RCTs

PRO Study, Location	Assessment Outcomes
General Health Measures	
EQ-5D-3L VAS ATTRACTION-3 ^{8,15} Multinational	Nivolumab showed significant overall improvement in QoL vs chemotherapy (at week 42, LS mean = 6.9; 95% CI 3.0-10.9; P=0.00069) Clinically meaningful changes (defined as change from baseline of seven points) were evident from week 18 through 30 Decreased risk of deterioration in QoL with nivolumab vs chemotherapy (HR 0.65, 95% CI 0.49–0.86, P=0.0030) Median time to deterioration was longer with nivolumab vs chemotherapy (4.3 months vs 2.7 months)
EQ-5D VAS KEYNOTE-181 ¹⁶ Multinational	HRQoL scores improved with pembrolizumab vs chemotherapy (LS mean change from baseline = 5.57; 95% CI 0.58-10.56)
Cancer Specific Measures	
EORTC QLQ-C30 KEYNOTE-181 ¹⁷ Multinational	No significant difference between pembrolizumab and chemotherapy arm At 9 weeks, GHS/QoL scores improved in 23%, stable in 42% and deteriorated in 34% patients in pembrolizumab group
EORTC QLQ-C30 ESCORT ⁷ , China	Lower risk of deterioration in symptoms in camrelizumab group vs chemotherapy from baseline to week 8
Disease-Specific Measures	
EORTC QLQ-OES18 KEYNOTE-181 ¹⁷ Multinational	No significant difference between pembrolizumab and chemotherapy arm
EORTC QLQ-OES18 ESCORT ⁷ , China	Lower risk of deterioration in symptom domains (reflux, taste problems, and coughing problems) from baseline to week 8 with camrelizumab vs chemotherapy

Indicates positive impact on HRQoL
Indicates no change in HRQoL
Abbreviations: EQ-5D-3L: EuroQoL 5-dimension 3-level; EQ-5D VAS: EuroQoL 5-dimension Visual Analogue Scale; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-OES18: EORTC Quality of Life Questionnaire - Esophageal Cancer Module; GHS/QoL: Global Health Status/ Quality of Life; HR: Hazard ratio; HRQoL: Health-related quality of life; LS: Least Squares; RCT: Randomized controlled trials

Figure 2 Health Utility Values by Disease Stage or Status Across Different Studies

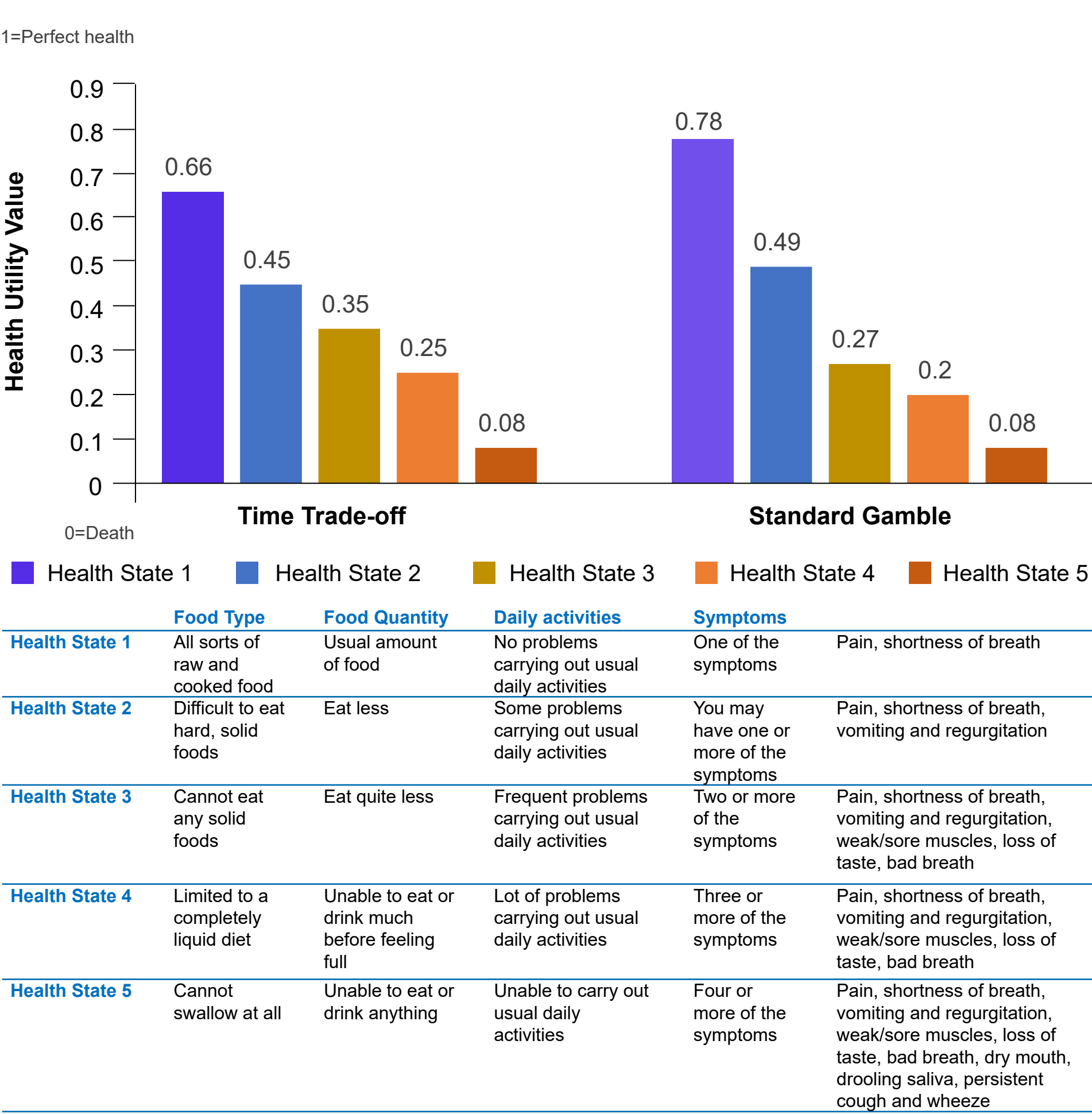


Disclosures
This study was funded by Novartis Pharmaceuticals Corporation, East Hanover, USA. Shruti Nambiar is ex-employee of Novartis. Ilia Ferrusi, Kavita Rodha and Manik Kalra are employees of Novartis. Dr. Elizabeth Smyth has received consulting, speaking, and/or research support from Novartis.
Copyright © 2022 Novartis Pharmaceuticals Corporation. All rights reserved.

Health Utilities

- Health utilities were reported in 7 studies (8 publications). Among these, 3 were observational studies and 4 were cost-effectiveness analysis studies
- Utility values were substantially lower (poorer HRQoL) in advanced stage compared to early-stage disease and healthy individuals (Figure 2)
- The utility values also decreased based on the state of disease progression in Stage IV EC patients (Figure 3)
- The health utility value substantially declines as the patient's health state worsens^{22,23} (Figure 3, refer supplementary file)

Figure 3 Health Utilities in EC Patients at Different Health States



Reference: McNamee 2004²², Retrospective study, UK
Abbreviations: EC: Esophageal Cancer

Conclusions

- There was a paucity of data on real-world humanistic burden in EC, particularly for advanced disease, and the available evidence was not easy to interpret for patients and clinicians. Despite the limited data, the humanistic burden of EC was evident
- HRQoL burden despite available treatments underscores the need for treatment modalities that can alleviate the humanistic impact of EC
- Studies comparing IO agents vs chemotherapy suggest that HRQoL could be less severely impacted in patients treated with IO agents
- Further research is needed to better characterize humanistic burden of EC. More reporting using standardized methods and at a granular level is suggested to achieve more robust conclusions

Limitations

- Most of the studies assessed HRQoL as a secondary or exploratory endpoint and thus the statistical methods used for evaluating HRQoL data were not adequately reported which made data interpretation a challenge
- There is a variation in sample size and study design, with most studies having a small sample size, retrospective design, and few RCTs

References

- Provided in supplementary file