RESEARCH ARTICLE

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Willingness to Pay for a Quality-Adjusted Life Year among Gastrointestinal Cancer Patients at a Tertiary Hospital of Vietnam, 2022

Binh Thang Tran^{1*}, Thi Tao Tran¹, Ngoc Quang La², Thi Thu Phuong Nguyen¹, Minh Hanh Nguyen³, Thi Minh Chau Huynh³, Hung Phuong Vu⁴

Abstract

Background: Gastrointestinal (GI) cancer burden in Asia is increasing, and Vietnam is no exception. Assessing the affordability of achieving a quality-adjusted life year (QALY) in gastrointestinal cancer patients Vietnam, as well as identifying predictors of willingness to pay (WTP) per QALY, is crucial to decision-making around medical intervention prioritization and performing medical technology assessments for these cancers. Objectives: Our study aimed to estimate WTP/QALY gained and associated factors among patients diagnosed with GI cancer at a tertiary hospital in Hue, Vietnam. **Methods:** A cross-sectional descriptive study, using contingent valuation methodology was conducted among 231 patients at tertiary hospital in 2022. A double limited dichotomous choice and the EQ-5D-5L were utilised to estimate WTP and QALY, respectively. Quantile regression was applied to determine predictors of WTP/QALY. **Results:** The mean and median maximum WTP/QALY gained among GI patients was \$15,165.6 (42,239.6) and \$4,365.6 (IQR: 1,586.5-14,552.0), respectively, which was equal to 3.68 times the 2022 gross domestic product (GDP) per capita in Vietnam. Additionally, cancer severity was found to have a significant impact on WTP per QALY gained, with a higher amount identified among patients with earlier stages of GI cancer. Furthermore, living in an urban dwelling and patients' treatment modalities were significantly associated with WTP/QALY. **Conclusion:** Evidence from our study can be used to inform how decision-makers in Vietnam to determine the cost-effectiveness of GI cancer interventions.

Keywords: Gastrointestinal cancer- WTP- QALY- Vietnam

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Introduction

Gastrointestinal (GI) cancer, spanning a broad range of digestive system cancer types, poses a significant public health concern as one of the most common cancers worldwide [1]. Colorectal, esophageal, gastric, liver, and pancreatic cancers are among the most common GI cancer types, many of which have a high prevalence in Asia [1, 2]. In Vietnam, the incidence of GI cancer has been reported to increase [3].

To date, the burden of GI cancer in Asia is increasing, contributed to by aging populations, population growth, high rates of risk behaviors such as smoking, and the high prevalence of H. pylori, HBV, and HCV infections [2]. In Vietnam, the burden of GI cancer has continued to rise, with cancer incidence tripling in the past 30 years [4]. Notably, changes in the diagnosis and treatment paradigm are known to have a great impact on cancer care and improve outcomes. However, cancer-attributable medical

costs have been reported to increase dramatically for patients and society [5]. For example, overall economic burden of colorectal cancer in 2018 was estimated approximately \$132.9 million (0.055% of the 2018 gross domestic product [GDP]) [6]. Debates among healthcare decision-makers surrounding the rapid advances in cancer drug development, and the high cost of these new therapies, have demonstrated a need for more cost-effectiveness analyses [7]. Evidence generated via these cost-effectiveness analyses can be used to inform both patient and healthcare system investments in cancer therapeutics [8].

One key method through which to evaluate the worth of a healthcare intervention is the measurement of quality-adjusted life years (QALYs). QALYs are often used in cost-effectiveness analyses to inform resource allocation decisions, by measuring how well a given medical treatment lengthens or improves a patient's life over time [9]. QALYs combine morbidity and mortality into a single

¹Faculty of Public Health, Hue University of Medicine and Pharmacy, Hue University, Hue, Vietnam. ²Department of Epidemiology, Hanoi University of Public Health, Hanoi, Vietnam. ³Oncology Center, Hue Central Hospital, Hue, Vietnam. ⁴School of Trade & International Economics, National Economics University, Hanoi, Vietnam. *For Correspondence: tranbinhthang@hueuni.edu.vn

metric, with corresponding quality-of-life weights ranging from 1.0 (perfect health) to 0.0 (death). The QALY serves as a convenient yardstick for measuring and comparing the health effects of different interventions, helping to promote consistency and transparency in healthcare decision-making [9].

In Vietnam, cost-effectiveness and/or cost-utility analyses have recently been used to assess and suggest medications for reimbursement in the public health insurance scheme. Interventions/programmes are considered cost-effective if the cost-effectiveness ratio increases below a certain cost threshold. This threshold is usually based on people's willingness to pay (WTP) for a QALY gained [10], which implies the maximum amount that a plan or governing body would pay to gain an extra year of perfect health. The paying body would then reimburse medications or procedures that have a lower incremental cost-effectiveness ratio (ICER) than the WTP/QALY threshold [11, 12]. However, there is currently no defined threshold in Vietnam; most measures follow the WHO recommendation, in which interventions are considered cost-effective if the ICER is between 1-3 GDPs per capita. Of course, the WTP/QALY may vary over time, and depends on the context. It is unlikely that there is a single, constant WTP/QALY [13]. Countries should develop decision-making processes that are customized to their unique circumstances, and which are supported by applicable laws, include local stakeholders, and are transparent, consistent, and just [14, 15]. While current reimbursement and coverage decision-making practices do involve patients and patient representatives in Vietnam to some extent, it is important to decide whether WTP should reflect a generic (public) or disease-specific (patient) perspective. These two options would like lead to different outcomes and have different implications for policymaking in general. To our knowledge, so far in Vietnam, only one study has been conducted on this topic, and it appears to be limited to non-small cell lung cancer [10]. Due to high burden of GI cancer, determining monetary value of a QALY and associated factors will provide important information for making medical technology assessments to prioritize medical interventions for these cancers in Vietnam. Thus, our study aimed to estimate the willingness to pay of a QALY gained among patients with gastrointestinal cancer and explore related factors at Hue Central Hospital (HCH) in Hue, Vietnam.

Materials and Methods

Study design and participants

This was a cross-sectional, descriptive study, using contingent valuation methodology to investigate the WTP/QALY among GI cancer patients at HCH, Vietnam. Patients were included in the study if they had a GI cancer diagnosis and were being treated at HCH at the time of the data collection period. GI cancer diagnoses were defined by their International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes, as follows: esophageal (C15.9), stomach (C16), colorectal (C18–20), liver (C22) and pancreatic bile duct cancers (C23–C24). Patients were included if during

interviews they were fully awake, able to communicate and could answer the questions, and voluntarily agreed to participate in the study.

Sample size was estimated proportion among people stated mean WTP greater than 1 GDP. Based on previous report in one study in Vietnam (79.0% patient with lung cancer was willing to pay for a QALY gained) [10], and a population size of 2000 GI inpatient per year, the study would require a sample size of 227 for estimating the expected proportion with 5% absolute precision and 95% confidence [16]. Finally, the total of 231 patients was included in the analysis. The samples were selected via convenience sampling during the study period due to time for approaching for our study and regulation of hospital. We interviewed all patients who met the selection criteria.

Setting and time of study

HCH is a tertiary hospital in central Vietnam and serves 15 million people across 14 provinces in the region. HCH's Oncology Center provides cancer-specific treatment services, such as chemotherapy, radiation therapy, and surgery, as well as provides technical support to other hospitals in the region. The data collection period for this study took place between September 2022–December 2022 at the HCH Oncology Center.

Variables and Measurement

The independent variables in this study included patients' demographic characteristics (age, gender, level of education, occupation, economic status, living area, health insurance copayment rate, comorbidities), GI cancer stage (I, II, III, IV), type of GI cancer (esophageal, stomach, colorectal, liver, pancreatic bile duct), type of treatment, days for delayed treatment, and health-related risk behaviors.

The dependent variable for the study was the WTP per QALY which involved three steps: 1) estimating the health improvement using a preference scale (QALY), 2) determining the WTP, and 3) combining these values to get the WTP per QALY.

The quality-adjusted life year (QALY)

The QALY is a measure of the quality of life related to a patient's health, taking into account both the duration and severity of their illness. The EQ-5D-5L is a widely used tool for assessing health-related quality of life, and is a questionnaire evaluating 5 dimensions of health: mobility, self-care, daily activities, pain/discomfort, and anxiety/ depression. Each dimension has 5 levels, ranging from 1 ("no problems") to 5 ("impossible"). The score for each dimension is then multiplied by a weight, i.e., a number reflecting the severity of the problem. The weights are determined by a survey of the general population, and vary by country. In Vietnam, the EQ-5D-5L score ranges from -0.5115 (worst possible health) to 1 (perfect health). The EQ-5D-5L is used in clinical trials, population surveys, and economic evaluations, and is a reliable and valid tool that has been shown to be responsive to changes in health status [17, 18]. In addition to the EQ-5D-5L, the EQ-VAS scale was also used in this study to ask patients to rate their present health on a scale of 0 (worst possible health) to

100 (best possible health).

Patient willingness to pay (WTP)

WTP is the maximum amount of money that a patient is willing to pay for a treatment or service. In this study, we used a double limited dichotomous choice (DLDC) method to assess patients' WTP for a new cancer treatment. The DLDC method is a well-established method for eliciting WTP data, and is considered to be reliable and mostly used over other methods in a recent systematic review [19], as it reduces the risk of patients understating or overstating their WTP [10]. Patients in this study were asked the following questions to assess their WTP for a hypothetical new cancer treatment:

• "Imagine that there is now a new treatment that cure your cancer and allow you to make a perfect recovery without any side effects. However, the treatment is not covered by health insurance, and you would have to pay for it yourself. Are you willing to pay 5 million VND per year for this type of treatment?"

The patients were then randomly assigned one of the following costs: 5 million VND, 10 million VND, 25 million VND, 40 million VND, 50 million VND, or 100 million VND. If the patient was willing to pay the cost that they were assigned, they were asked a follow-up question with a higher cost. If the patient was not willing to pay the cost assigned, they were asked a follow-up question with a lower cost was asked. After this process, all patients were asked the open-ended question:

• "What is the maximum price you are willing to pay each year for this type of treatment?"

WTP per QALY was estimated using the following

 Maximum value of WTP/QALY = maximum value of WTP / (1 – current health state EQ 5D-5L utility)

Threshold of WTP/QALY are classified into groups based on the average income of Vietnamese people in 2022 (GDP per capita: \$4110) [20] with the following groups: <1 GDP, <2 GDP, <3 GDP; >=3 GDP. Currency was used in US dollars (exchange rate: VND 23,260 ~ \$ 1).

Data collection

At the start of each interview, patients were asked whether they voluntarily consented to participate in the study. Interviews were conducted in a private room within the health department where they were currently receiving treatment. Interviewers were sixth-year Preventative Medicine program students and fourth-year Public Health program students. Interviews were conducted face-to-face with a structured questionnaire and were combined with references to medical records at the hospital department. Cancer stages of cancer and types of cancer were confirmed by oncologists and pathologists at HCH. Secondary data was collected from patient medical records and/or bills.

Data analysis

Data was entered and managed using Microsoft Excel (2018), and analyses were performed using Stata 16.0. The significance level was established at p < 0.05. Qualitative

variables were presented as numbers (n) and percentages, and quantitative variables were presented as means (standard deviations [SD]) or medians. The relationship between patients' general information, family-related factors, disease status, and willingness to pay for a year of quality-adjusted life (WTP/QALY) was determined using chi-squared or Fisher's exact tests. A multivariate quantile regression model was used to determine factors associated with WTP/QALY (at percentiles of 25%, 50%, and 75%). The perfect health state was excluded from analysis [21]. The consistency of the relationship between EQ-VAS and EQ 5D-5L was also investigated (r=0.7052, p<0.001)).

Research Ethics

The study protocol was approved by the Biomedical Ethics Committee of the University of Medicine and Pharmacy, Hue University (No.H2022/485, dated on 30 June 2022), and by the Director's Board of the Oncology Centre and Hue Central Hospital. Informed consent was obtained from participants prior to conducting the study; participants were fully informed of the study's purpose, confidentiality, and time required to complete the questionnaire before deciding whether to participate.

Results

Characteristics of the study population are summarized in Table 1. The majority of patients were male (80.1%), and the largest proportion of patients were aged between 60-69 years (35.1%). More than half of patients were married (93.5%), atheist or non-religious (81.4%), lived in a rural area (77.5%), and/or had completed middle or high school (57.6%). Among patients who reported on their risk behaviors, 55.0% and 64.6% reported being smokers and drinkers, respectively. A considerable proportion of patients also worked in an occupation with an unstable income (53.7%). Almost all patients reported having health insurance. Average monthly patient incomes during the one month before and after cancer diagnosis were \$217.04±234.8 and \$46.56±138.23, respectively.

Among 231 patients with GI cancer, colorectal cancer accounted for the highest proportion (48.5%), followed by esophageal cancer (30.7%). The highest proportions of patients were diagnosed with stage III and stage IV cancers at 35.9% and 48.5%, respectively. Surgery and chemotherapy were the main treatment regimens that patients reported having received (48.5%). Comorbidities were observed in 28.6% of patients. Across patients, the mean time from diagnosis to treatment for the patients was 11.45 ± 67.34 days. Only 7.8% of respondents did not receive treatment immediately following diagnosis (Table 2). Outstanding problems were frequently reported among patients, including pain/discomfort (79.2%), anxiety/depression (77.9%), and problems participating in daily activities (64.9%; Table 3). The mean EQ 5D and EQ VAS instrument scores were about 0.649 and 0.5, respectively.

The mean and median WTP/QALY (EQ 5D) across patients were \$15,165.6 (42,239.6) and \$4,365.6 (1,586.5-14,552.0), respectively. Patients with advanced stages of GI cancer showed a higher WTP/QALY compared with

Table 1. Demographic and Socioeconomic Characteristics of Study Population Stratified by GDP Group (n=231)

	Total ^a n (%)	< 1 GDP n=111	$\geq 1 \text{ GDP}$ n=120	p-valu
Sex	(/0)		1120	0.72
Males	185 (80.1)	90 (48.6)	95 (51.4)	
Females	46 (19.9)	21 (45.7)	25 (54.3)	
Age group	,	,	,	0.54
<50	42 (18.2)	23 (54.8)	19 (45.2)	
50-59	72 (31.2)	30 (41.7)	42 (58.3)	
60-69	81 (35.1)	41 (50.6)	40 (49.4)	
≥70	36 (15.6)	17 (47.2)	19 (52.8)	
Mean±SD	59.0 (11.2)	59.1 (11.8)	58.9 (10.6)	0.93
Religion	, ,	, ,	, ,	0.37
No	188 (81.4)	93 (49.5)	95 (50.5)	
Other	43 (18.6)	18 (41.9)	25 (58.1)	
Living area	- ()		()	0.059
Rural	179 (77.5)	92 (51.4)	87 (48.6)	
Urban	52 (22.5)	19 (36.5)	33 (63.5)	
Marital status	,	,	,	0.91
Single/ Divorced/ Widow	15 (6.5)	7 (46.7)	8 (53.3)	
Married	216 (93.5)	104 (48.1)	112 (51.9)	
Education	,	,	,	0.16
Less than elementary/ Elementary	72 (31.2)	40 (55.6)	32 (44.4)	
Elementary Middle School-High School	133 (57.6)	62 (46.6)	71 (53.4)	
College/ Undergraduate, post graduate	26 (11.3)	9 (34.6)	17 (65.4)	
Occupation ^b	- (-)	()	, ()	0.23
Have a stable income (civil servants/officers, workers, pensioners)	50 (21.6)	19 (38.0)	31 (62.0)	
Have an unstable income (jobs such as farming, trading, nired labor, self-employed)	124 (53.7)	65 (52.4)	59 (47.6)	
No income (housewife, lost strength)	57 (24.7)	27 (47.4)	30 (52.6)	
Economic status				0.67
Low (Poor/ Near poor)	33 (14.3)	17 (51.5)	16 (48.5)	
High	198 (85.7)	94 (47.5)	104 (52.5)	
Living alone				0.92
Yes	6 (2.6)	3 (50.0)	3 (50.0)	
No	225 (97.4)	108 (48.0)	117 (52.0)	
Level of health insurance benefits (%)				0.89
80	89 (38.5)	41 (46.1)	48 (53.9)	
95	29 (12.6)	14 (48.3)	15 (51.7)	
100	113 (48.9)	56 (49.6)	57 (50.4)	
Income lost due to COVID-19 (one month)				0.98
No	81 (35.1)	39 (48.1)	42 (51.9)	
Yes	150 (64.9)	72 (48.0)	78 (52.0)	
Monthly income before cancer diagnosis (\$ US)	217.05 (234.80)	191.22 (222.21)	240.936 (244.37)	0.11
Monthly income after a cancer diagnosis (\$ US)	46.56 (138.23)	30.41 (96.37)	61.515 (166.96)	0.087
Smoking status				0.065
Yes	127 (55.0)	68 (53.5)	59 (46.5)	
No	104 (45.0)	43 (41.3)	61 (58.7)	
Alcohol consumption				0.42
Yes	150 (64.9)	75 (50.0)	75 (50.0)	
No	81 (35.1)	36 (44.4)	45 (55.6)	

^a, Data are presented as mean (SD) or median (IQR) for continuous measures, and n (%) for categorical measures; ^b, Participants with stable income include civil servants/officers, workers, pensioners. Individuals with jobs such as farming, trading, hired labor, self-employed classified as an having unstable income. Housewife was considered to have no income.

Table 2. Information Related to Cancer of Participants Stratified by GDP Group

	Total ^a	< 1 GDP	≥ 1 GDP	p-value
Type of cancers				0.24
Liver-biliary-pancreatic cancer	16 (6.9)	10 (62.5)	6 (37.5)	
Stomach cancer	32 (13.9)	19 (59.4)	13 (40.6)	
Colorectal cancer	112 (48.5)	48 (42.9)	64 (57.1)	
Esophagus cancer	71 (30.7)	34 (47.9)	37 (52.1)	
Cancer stages				0.6
I	4 (1.7)	1 (25.0)	3 (75.0)	
II	32 (13.9)	14 (43.8)	18 (56.3)	
III	83 (35.9)	38 (45.8)	45 (54.2)	
IV	112 (48.5)	58 (51.8)	54 (48.2)	
Cancer treatment modalities				0.11
Surgery	3 (1.3)	2 (66.7)	1 (33.3)	
Surgery and chemotherapy	112 (48.5)	44 (39.3)	68 (60.7)	
Chemotherapy	62 (26.8)	35 (56.5)	27 (43.5)	
Radiotherapy	1 (0.4)	1 (100.0)	0 (0.0)	
Palliative care	53 (22.9)	29 (54.7)	24 (45.3)	
Comorbidities				0.93
No	165 (71.4)	79 (47.9)	86 (52.1)	
Yes	66 (28.6)	32 (48.5)	34 (51.5)	
Treat immediately afte being diagnosed				0.86
No	18 (7.8)	9 (50.0)	9 (50.0)	
Yes	213 (92.2)	102 (47.9)	111 (52.1)	
Delayed treatment				0.95
No	212 (91.8)	102 (48.1)	110 (51.9)	
Yes	19 (8.2)	9 (47.4)	10 (52.6)	
Time for delayed treatment (Days)	11.45 (67.34)	9.324 (39.963)	13.417 (85.329)	0.65
EQ 5D-5L Utilities (Mean±SD)	0.649 (0.285)	0.519 (0.325)	0.769 (0.169)	< 0.001
EQ 5D-5L Utilities (median, IQR)	0.734 (0.552-0.852)	0.565 (0.365-0.726)	0.806 (0.729-0.852)	< 0.001
EQ VAS (Mean±SD)	0.538 (0.180)	0.4820 (0.1184)	0.590 (0.159)	< 0.001
EQ VAS (median, IQR)	0.500 (0.400-0.700)	0.500 (0.400-0.600)	0.600 (0.500-0.700)	< 0.001
WTP/QALY (VAS) (Mean±SD)	11,784.6 (39,927.2)	2,296.60 (3,108.73)	20,560.96 (53,950.14)	< 0.001
WTP/QALY (VAS) (median, IQR)	4,298.7 (1,432.9-8,597.3)	1,432.89 (429.87-2,865.78)	7,164.45 (4,298.67-13,863.22)	< 0.001
WTP/QALY (EQ 5D) (Mean±SD)	15,165.6 (42,239.6)	1,613.84 (1,239.58)	27,701.03 (55,832.25)	< 0.001
WTP/QALY (EQ 5D) (median, IQR)	4,365.6 (1,586.5-14,552.0)	1,362.93 (475.31-2,545.85)	12,612.82 (7,993.84-24,833.46)	< 0.001
WTP/QALY (GDP catergory) (n, %)				
< 1 GDP	111 (48.1)			
1 to <2 GDP	32 (13.9)			
2 to <3 GDP	27 (11.6)			
>=3 GDP	61 (26.4)			

^a, Data are presented as mean (SD) or median (IQR) for continuous measures, and n (%) for categorical measures.

those with earlier stages (\$ 16,118.32 vs. \$ 10,005.2, respectively). The median WTP/QALY was highest among stage I patients (Table 3). The percentage of WTP/QALY defined by using GDP per capita is presented in Figure 1.

Across patients, a total of 59.7% expressed their WTP/ QALY with an amount higher 1 GDP. In this group, there was a higher proportion of patients with early cancer stages (75.0% and 56.3% for stage 1 and stage II, respectively) compared with those with late stages (54.2% for stage III and 48.2% for stage IV) (Figure 1).

A multivariate quantile regression model was conducted to examine the factors associated with amount of WTP/QALY at 25th, 50th, and 75th percentiles (Table 4). At the 25th percentile, the model indicated that patients residing in urban dwellings were willing to pay significantly higher than patients in rural areas with coefficient of 2002 (95% CI=593-3411.1, p=0.006), and patients with stage IV cancers were willing to pay significantly less than those with stage I with coefficient and 95%CI: -4,417.1(-8,645.5 to -188.6), p=0.041. Meanwhile, at the 50th percentile, stage II, stage III, and stage IV cancers were significantly associated with WTP/QALY with coefficient and 95%CI: stage II (-12,168.3(-24,024.3 to -312.3), p=0.044; stage III: -15,103.6(-26,459.9 to -3747.4), p=0.009; and stage IV: -16,361(-27,813 to -4,909), p=0.005. In addition, cancer

Table 3. Percentage of each EQ-5D-5L Dimension, Utility Score, and WTP by Cancer Stages (n=231)

	Cancer stages					
EQ 5D-5L	All	I	II	III	IV	
Mobility (n, %)*	126 (54.5)	3 (75.0)	13 (40.6)	38 (45.8)	72 (64.3)	
Self-care (n, %)*	126 (54.5)	3 (75.0)	15 (46.9)	37 (44.6)	71 (63.4)	
Usual activities (n, %)**	150 (64.9)	4 (100.0)	16 (50.0)	44 (53.0)	86 (76.8)	
Pain/discomfort (n, %)	183 (79.2)	3 (75.0)	24 (75.0)	64 (77.1)	92 (82.1)	
Anxiety/depression (n, %)	180 (77.9)	3 (75.0)	24 (75.0)	64 (77.1)	89 (79.5)	
Utility score						
Mean (SD)**	0.649 (0.285)	0.645 (0.177)	0.722 (0.211)	0.720 (0.195)	0.576 (0.340)	
Median (IQR)*	0.734 (0.552-0.852)	0.651 (0.506-0.784)	0.805 (0.669-0.852)	0.783 (0.577-0.852)	0.669 (0.429-0.820)	
EQ VAS Mean (SD)	0.538 (0.180)	0.525 (0.126)	0.575 (0.148)	0.564 (0.161)	0.508 (0.199)	
Median (IQR)	0.500 (0.400-0.700)	0.500 (0.450-0.600)	0.600 (0.475-0.675)	0.600 (0.500-0.700)	0.500 (0.30-0.675)	
WTP/QALY (EQ VAS) Mean (SD)	11,784.58 (39,927.21)	6,161.43 (4,729.26)	5,213.87 (5,393.10)	15,465.28 (58,294.98)	11,135.08 (27,566.86)	
Median (IQR)	4,298.67 (1,432.89-8,597.34)	6,591.30 (3,009.07-9,313.79)	4,298.67 (788.09-6,806.23)	4,298.67 (1,791.11-8,597.34)	3,438.94 (1,432.89-9,672.01)	
WTP/QALY (EQ 5D) Mean (SD)	15,165.62 (42,239.59)	11,119.18 (9,529.54)	9,865.95 (11,119.36)	11,617.00 (17,784.60)	19,454.12 (58,220.74)	
Median (IQR) Median (IQR)	4,365.61 (1,586.46-14,552.04)	11,383.13 (3,555.98-18,682.38)	8,577.24 (1,288.51-14,981.01)	4,365.61 (2,091.61-12,112.35)	3,942.84 (1,465.32-13,991.24)	

^{**,} p<0.001; *, p<0.05; *, p<0.01; EQ VAS was converted to range 0 to 1 by dividing by 100

treatment modalities were also associated with WTP/QALY at the 75th percentile, with coefficient and 95%CI: surgery and chemotherapy: -54,363.3 (-100,944.4 to -7,782.1), p=0.022; chemotherapy: -56,935.2 (-104014.9 to -9,855.5), p=0.018; palliative care: -62,175.2 (-109,384.2 to -14,966.3), p=0.01), respectively.

Discussion

In our study of 231 GI cancer patients, we observed predictors of WTP/QALY by percentile, and determined

the mean and median of WTP/QALY to be \$15,165.6 (42,239.6), \$4,365.6 (IQR: 1,586.5-14,552.0), respectively. We also investigated predictors of WTP/QALY, which included urban dwelling, cancer stage at diagnosis, and treatment modality.

Historically, monetary value per QALY gained bears considerable weight in decision-making around healthcare interventions across treatment areas. Previous studies have explored this influence; for example, a 2015 study among lung cancer patients in Thailand found that both low-income patients and the general public had a WTP

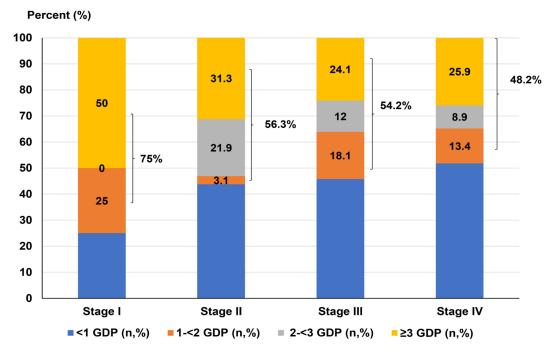


Figure 1. Distribution of Willingness to Pay (WTP) for a Quality-Adjusted Life (QALY) Gained by Threshold Using Gross Domestic Product (GDP) per Capita in Vietnam 2022, GDP per Capita: \$ 4110.

Alcohol consumption (Ref= Yes) Smoking status (Ref= Yes) Factors Cancer stages (Ref = Stage I) Delayed treatment (Ref= No) Income lost due to COVID-19 (one month) Yes vs No Level of health insurance benefits (%) (Ref=80%) Living area (Ref=Rural) Occupation (Ref= Have a stable income) ∃conomic status (Ref≒Low) Education (Ref= Less than elementary/ Elementary) Age group (Ref=<50) Type of cancers (Ref = Liver-biliary-pancreatic cancer) Gender (Ref=Male) 95 60-69 VI Ξ ≥70 50-59 Treat immediately after being diagnosed Esophagus cancer Colorectal cancer Stomach cancer Have an unstable income College/ Undergraduate, post graduate Elementary Middle School-High School Female .4417.1(-8645.5 to -188.6) -3457.6(-7650.7 to 735.5) 331.8(-1351.1 to 2014.6) -216.8(-2987.8 to 2554.1) -1079.1(-2299.9 to 141.8) 854.8(-1195.3 to 2904.9) -485.9(-2247.2 to 1275.4) .3909.2(-8286.8 to 468.4) -729.5(-2134.8 to 675.8) -187(-2760.1 to 2386.2) .222.2(-2643.8 to 2199.4) 116.2(-1587.1 to 1819.6) 818.5(-711.2 to 2348.1) 297.1(-974.7 to 1568.8) .824.4(-2870.6 to 1221.7) 39.3(-1629.7 to 1708.3) .865.3(-3366.2 to 1635.6) 520.1(-818.6 to 1858.7) 3.1(-1997.7 to 2003.8) -299(-2586.3 to 1988.3) 1602.5(-3502.8 to 297.8) 2002 (593 to 3411.1) Percentile at 25% 0.886 0.857 0.293 0.646 0.083 0.412 0.587 0.445 0.797 0.041 0.106 0.307 0.878 0.998 0.8930.428 0.0060.9630.496 0.698 0.0980.08 0.8 -15103.6(-26459.9 to -3747.4) -12168.3(-24024.3 to -312.3) -1020.2(-6438.8 to 4398.3 -1496.2(-4802.7 to 1810.2) -2146.7(-7699.1 to 3405.6) .3027.8 (-7797.8 to 1742.3) 2086.1(-1730.1 to 5902.2) -401.2(-7905.7 to 7103.3) 778.2 (-2666.2 to 4222.5) -1102(-5622.2 to 3418.2) -342.1(-4899.8 to 4215.6) -16361(-27813 to -4909) 344.4(-6214.1 to 6902.9) 424.6(-4188.6 to 5037.7) -3024.4(-8566 to 2517.2) 699.1(-5495.6 to 6893.8) 452.7(4258.7 to 3353.3) 708.4(-3434.3 to 4851.1) 875.3(-2750.2 to 4500.8) ·192.3(-5339.1 to 4954.4) 92.8(-4499.8 to 4685.3) 395.7(-6377.7 to 7169) 1393(-5576 to 8362) ß, 95%CI Percentile at 50% 0.044 0.736 0.212 0.009 0.918 0.711 0.373 0.447 0.6310.9080.6350.824 0.882 0.9410.0050.6940.916 0.8560.6560.2830.2820.968-5186.2 (-21402.4 to 11030.0) -6132.5(-31644.7 to 19379.7) -4578.3(-23453.9 to 14297.4) 5671.2(-33260.9 to 44603.3) -2047.4(-42352.9 to 38258.1 3328.3(-12038.6 to 18695.2) 2177.9(-13316.3 to 17672.2) 4586.5(-12910.2 to 22083.2) -650.8(-39257.2 to 37955.6) 3469.3(-22308.4 to 15369.8) 1469.9(-19589.4 to 22529.3) 6463.8(-6475.1 to 19402.7) -1532.7(-25224.4 to 22159) 1751.4(-9489.3 to 12992.1) 1852.5(-11120.7 to 14825.8) -412.8(-22709 to 21883.4) -562 (-18982.8 to 17858.9) -693.6(-14777 to 13389.9) 6231(-16795.5 to 29257.6) 6924(-8688.6 to 22536.7) 1733(-13949.9 to 17415.8) -507.2(-12832.4 to 11818) 297.1(-974.7 to 1568.8) ß, 95%CI Percentile at 75% 0.774 0.974 0.971 0.8280.9230.887 0.759 0.779 0.6330.5290.5940.9350.8910.3830.782 0.6060.8990.6360.952 0.717 0.3260.920.67 p

Table 4. Multivariate Quantile Regression Model: factors associtaed associated with the willingness to pay (WTP) for a quality-adjusted life (QALY) gained (US dollar)

Percentile at 25% (\$ 1,586.5); Percentile at 50% (\$ 4,365.6); Percentile at 75% (\$ 14,552.0); Ref, reference group Table 4. Continued Cancer treatment modalities (Ref=Surgery Factors Comorbidities (Ref=No) Radiotherapy Surgery and chemotherapy Palliative care Chemotherapy 4709.2(-2318.9 to 11737.3) -142.9(-5256.3 to 4970.5) 2442.7(-2616.6 to 7501.9) 1143.5(-3983.9 to 6270.9) 946.7(-8849.6 to 10743) 49.9(-1197.5 to 1297.3) ß, 95%CI Percentile at 25% 0.849 0.956 0.661 0.342 0.188J -1154.9(-15003.5 to 12693.8) -710.8(-27242.4 to 25820.9) 3782.8(-9919.3 to 17484.8) 20949.5(1915.3 to 39983.7) -1504.1(-4882.5 to 1874.2) 1275.5(-12611.2 to 15162.2) ß, 95%CI Percentile at 50% 0.958 0.587 0.0310.856 0.3810.87 -62175.2(-109384.2 to -14966.3 -63709.5(-153905.9 to 26486.9) -56935.2(-104014.9 to -9855.5) -54363.3(-100944.4 to -7782.1) -3170.5(-14655.4 to 8314.5) 67304.6(2596.2 to 132013) ß, 95%CI Percentile at 75% 0.165 0.018 0.022 0.587 0.01

that exceeded the acceptability threshold by more than double (\$5,123) [22]. In a similar study conducted among Malaysian population, the estimated value for the costeffectiveness threshold was \$9,000 [23]. Furthermore, a meta-analysis of 54 studies evaluating WTP for cancer treatment and outcomes indicated that QALY exhibits the highest WTP (\$11,498-\$ 589,822) compared to 1-year survival, quality of life improvement, and pain reduction

In particular, comparing our findings with those of other studies proves challenging due to variations in sociodemographic factors and the burden of cancer in different countries. A recent study reviewed all studies on WTP values for cancer treatments that reported the highest WTP values were for a quality-adjusted life year (QALY) ranged: \$11,498-\$589,822 [24]. In Vietnam, only one study has been conducted analyzing the WTP/ QALY gained among cancer patients thus far. In this 2020 study conducted among 400 advanced nonsmall cell lung cancer patients across 6 Vietnamese hospitals, patients were willing to pay \$11,301 for one QALY gained [10]. Notably, this WTP is lower than that found in our study. We found that the monetary value per QALY gained is equivalent to 3.68 times the GDP per capita in Vietnam in 2022, compared with 4.4 GDP per capita in Vietnam in 2017 in the aforementioned study [10]. Similarly, our study indicated a higher WTP/QALY level compared to the level observed in the general population in rural areas in Vietnam in 2012 (\$667–993) [10].

We found that patients who live in urban dwellings tended to indicate a higher WTP for health services, consistent with the extensive evidence that WTP/QALY increases with the a subject's wealth or economic status [25]. WTP was also found to vary depending on patient disease severity in our study, consistent with two previous Vietnamese studies that identified the significant associations between both hemophilia A and asthma severity with WTP/QALY [26, 27]. Previous literature has also documented the relationship between health states and WTP/QALY; a 2013 study in Japan found an association between higher WTP/QALY and worse health states [28]. Similarly, in a recent study among Iranian patients, the most severe diseases were associated with the lowest health values and the highest mean WTP values [29]. WTP has been consistently found to be higher for participants with more severe illnesses across studies; therefore, health condition severity plays a key role in decision-making [28, 30, 31]. For example, severity is an important factor in measuring "burden of illness". Under a value-based pricing approach in the UK, diseases with a higher burden of illness would be associated with higher thresholds [28]. However, in our study, the opposite trend was observed: we identified a negative association between disease severity and WTP. Although cancer drugs contribute significantly to improvement towards progression-free survival, high cancer drug prices have posed considerable barriers including patient financial burden and distress [32]. The accumulation of out-of-pocket costs from the time of first diagnosis, the erosion of financial resources and non-medical household expenditures, and lack of accessible and effective coping strategies for patients all

contribute to subjective financial distress [32]. Financial burden is substantial and considered to be a barrier to assess to cancer treatment in developing countries. In Vietnam, households with non-communicable diseases (including cancer) were found to be 2.3 times more susceptible to poverty as a result of healthcare payments compared to other households [33]. Specifically, treatment costs pushed 37.4% of households in which cancer patients were residing under the poverty line [33]. Additionally, financial hardship was reported in 68.0% of cancer patients in Vietnam, which is higher compared with countries in the same region, such as Malaysia, Laos, and Thailand [34].

Further, ability to pay was found to be impacted by the patient's stage of cancer; aligning with previous findings that medical costs associated with cancer diagnoses and treatments are higher among patients with advanced cancer stages [35, 36, 6]. In the context of these findings, it is reasonable to infer that patients who are diagnosed at an early stage tend to pay a higher amount per QALY gained in our study. This reflects the high valuation of early diagnosis, including more effective treatment, improved survival, increased QALY, and reduced treatment costs

Notably, we also observed a variation in WTP/QALY between GDP groups. Half of patients in our study were willing to pay an amount less than one GDP per capita in Vietnam in 2022. The cost of general health conditions can be calculated by GDP per capita or by WTP/QALY to determine the threshold for insurance reimbursement [38]. To date, the correlation between using the WHO threshold for policy-making and GDP per capita is a matter of debate [38]. Because the rationale for using GDP per capita as a criterion is unclear, in a 2016 study Woods et al. estimated the thresholds to be 0.1–0.51 and 0.18–0.71 GDP per capita for low- and middle-income countries and middle- and high income countries, respectively [39]. However, basing these thresholds on GDP may be inappropriate and fail to capture other influences; therefore, considering country-specific societal priorities is recommended to generate national threshold values [29, 13, 15]. Furthermore, thresholds can be identified based on patient preferences, and could effectively serve as a criterion to indicate general acceptability for a given disease treatment [38]. Findings from our study can be used to inform the development of a threshold that decision-makers can utilize to identify whether an intervention is cost-effective for GI cancer treatment in Vietnam.

Our study has limitations due to the sampling method employed. Convenience sampling was ultilised to recruit participants for our study. Consequently, our findings may be biased in selection and limit the generalizability of our findings to the national population. Additionally, the study was conducted at a single tertiary referral hospital (central level), which primarily treats patients in advanced stages of the disease (82.7% compared to 62.5% in a specialized provincial hospital [40]). Future studies with more representative sampling are needed to elucidate our findings.

In conclusion, the WTP/QALY among Vietnamese

GI cancer patients was determined to be \$15,165.6 (42,239.6), or 3.68 GDP per capita in 2022 in our study. We identified that cancer severity had a significant impact on the monetary value of a QALY gained, implying that the threshold should be adjusted according to cancer severity in order to better align with patients' preferences. These findings may inform the evaluation of healthcare interventions for GI cancer in Vietnam. Further research on WTP/QALY is needed to gain a comprehensive understanding of WTP for specific cancers in Vietnam.

Author Contribution Statement

All authors contributed equally in this study.

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Research Ethics

The study protocol was approved by the Biomedical Ethics Committee of the University of Medicine and Pharmacy, Hue University (No.H2022/485, dated on 30 June 2022), and by the Director's Board of the Oncology Centre and Hue Central Hospital. Informed consent was obtained from participants prior to conducting the study; participants were fully informed of the study's purpose, confidentiality, and time required to complete the questionnaire before deciding whether to participate.

References

- 1. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology. 2020;159(1):335-49.e15. https://doi.org/10.1053/j.gastro.2020.02.068.
- 2. Pourhoseingholi MA, Vahedi M, Baghestani AR. Burden of gastrointestinal cancer in asia; an overview. Gastroenterol Hepatol Bed Bench. 2015;8(1):19-27.
- 3. Pham DX, Phung AHT, Nguyen HD, Bui TD, Mai LD, Tran BNH, et al. Trends in colorectal cancer incidence in ho chi minh city, vietnam (1996-2015): Joinpoint regression and age-period-cohort analyses. Cancer Epidemiol. 2022;77:102113. https://doi.org/https://doi.org/10.1016/j. canep.2022.102113.
- 4. Pham T, Bui L, Kim G, Hoang D, Tran T, Hoang M. Cancers in vietnam-burden and control efforts: A narrative scoping review. Cancer Control. 2019;26(1):1073274819863802. https://doi.org/10.1177/1073274819863802.
- 5. Toscano F, Vera A, Kim E, Golinelli D, Vila-Reyes H, Bteich F, et al. The role of cost-effectiveness analysis in patientcentered cancer care in the era of precision medicine. Cancers (Basel). 2021;13(17). https://doi.org/10.3390/ cancers13174272.
- 6. Tran BT, Choi KS, Nguyen TX, Sohn DK, Kim SY, Suh JK, et al. The direct and indirect costs of colorectal cancer in vietnam: An economic analysis from a social perspective. Int J Environ Res. 2021;18(1):12.
- 7. Cherla A, Renwick M, Jha A, Mossialos E. Cost-effectiveness of cancer drugs: Comparative analysis of the united states and england. EClinicalMedicine. 2020;29. https://doi. org/10.1016/j.eclinm.2020.100625.

- 8. Barr HK, Guggenbickler AM, Hoch JS, Dewa CS. Real-world cost-effectiveness analysis: How much uncertainty is in the results? Curr Oncol. 2023;30(4):4078-93. https://doi.org/10.3390/curroncol30040310.
- 9. Woodward RM, Menzin J, Neumann PJ. Quality-adjusted life years in cancer: Pros, cons, and alternatives. Eur J Cancer Care (Engl). 2013;22(1):12-9. https://doi.org/10.1111/ecc.12006.
- 10. Ha TV, Hoang MV, Vu MQ, Hoang NT, Khuong LQ, Vu AN, et al. Willingness to pay for a quality-adjusted life year among advanced non-small cell lung cancer patients in viet nam, 2018. Medicine (Baltimore). 2020;99(9):e19379. https://doi.org/10.1097/md.0000000000019379.
- 11. Bazarbashi S, De Vol EB, Maraiki F, Al-Jedai A, Ali AA, Alhammad AM, et al. Empirical monetary valuation of a quality-adjusted life-year in the kingdom of saudi arabia: A willingness-to-pay analysis. Pharmacoeconomics open. 2020;4(4):625-33. https://doi.org/10.1007/s41669-020-00211-0.
- 12. Tran BT, Choi KS, Sohn DK, Kim S-Y, Suh JK, Tran TH, et al. Estimating cost-effectiveness of screening for colorectal cancer in vietnam. Expert Rev Pharmacoecon Outcomes Res. 2021;21(6):1211-20.
- 13. Kazibwe J, Gheorghe A, Wilson D, Ruiz F, Chalkidou K, Chi YL. The use of cost-effectiveness thresholds for evaluating health interventions in low- and middle-income countries from 2015 to 2020: A review. Value Health. 2022;25(3):385-9. https://doi.org/10.1016/j.jval.2021.08.014.
- Ben-Aharon O, Iskrov G, Sagy I, Greenberg D. Willingness to pay for cancer prevention, screening, diagnosis, and treatment: A systematic review. Expert Rev Pharmacoecon Outcomes Res. 2023;23(3):281-95. https://doi.org/10.1080 /14737167.2023.2167713.
- Leech AA, Kim DD, Cohen JT, Neumann PJ. Use and misuse of cost-effectiveness analysis thresholds in low- and middle-income countries: Trends in cost-per-daly studies. Value Health. 2018;21(7):759-61. https://doi.org/10.1016/j. jval.2017.12.016.
- Daniel WW, Cross CL. Biostatistics: a foundation for analysis in the health sciences. Wiley; 2018 Nov 13.
- Mai VQ, Sun S, Minh HV, Luo N, Giang KB, Lindholm L, et al. An eq-5d-5l value set for vietnam. Qual Life Res. 2020;29(7):1923-33. https://doi.org/10.1007/s11136-020-02469-7.
- 18. Tran BT, Pham NH, Nguyen TX, Choi KS, Sohn DK, Kim S-Y, et al. Measurement of health-related quality of life among colorectal cancer patients using the vietnamese value set of the eq-5d-5l. Patient prefere adherence. 2020:2427-37.
- 19. Nu Vu A, Hoang MV, Lindholm L, Sahlen KG, Nguyen CTT, Sun S. A systematic review on the direct approach to elicit the demand-side cost-effectiveness threshold: Implications for low- and middle-income countries. PLOS ONE. 2024;19(2):e0297450. https://doi.org/10.1371/journal.pone.0297450.
- Vietnam General Statistics Office. Socio-economic situation report in the fourth quarter and 2022. Hanoi: Vietnam General Statistics Office, 2023.
- 21. Martín-Fernández J, Polentinos-Castro E, del Cura-González MI, Ariza-Cardiel G, Abraira V, Gil-LaCruz AI, et al. Willingness to pay for a quality-adjusted life year: An evaluation of attitudes towards risk and preferences. BMC Health Serv Res. 2014;14(1):1-10.
- 22. Thongprasert S, Crawford B, Sakulbumrungsil R, Chaiyakunapruk N, Petcharapiruch S, Leartsakulpanitch J, et al. Willingness to pay for lung cancer treatment: Patient versus general public values. Int J Technol Assess Health Care. 2015;31(4):264-70. https://doi.org/10.1017/

- s0266462315000409.
- 23. Shafie AA, Lim YW, Chua GN, Hassali MA. Exploring the willingness to pay for a quality-adjusted life-year in the state of penang, malaysia. Clinicoecon Outcomes Res. 2014;6:473-81. https://doi.org/10.2147/ceor.S67375.
- 24. Yong ASJ, Lim YH, Cheong MWL, Hamzah E, Teoh SL. Willingness-to-pay for cancer treatment and outcome: A systematic review. Eur J Health Econ. 2022;23(6):1037-57. https://doi.org/10.1007/s10198-021-01407-9.
- 25. Martín-Fernández J, Polentinos-Castro E, del Cura-González MI, Ariza-Cardiel G, Abraira V, Gil-LaCruz AI, et al. Willingness to pay for a quality-adjusted life year: An evaluation of attitudes towards risk and preferences. BMC Health Serv Res. 2014;14(1):287. https://doi.org/10.1186/1472-6963-14-287.
- Huynh Thi Minh Anh, Nguyen Thi Xuan Lieu, Pham Anh Tuan, Thuy NTT. Willingness-to-payper quality-adjusted life year of patients with asthma in district 11 hospital. Vietnam Medical Journal. 2021;505(2). https://doi.org/10.51298/ vmj.v505i2.1125.
- 27. Vo Ngoc Yen Nhi, Thuy NTT. Willingness-to-pay per quality- adjusted life year of patients with hemophilia a in national institute of hematology and blood transfusion in 2022. Vietnam Medical Journal. 2022;516(2). https://doi.org/10.51298/vmj.v516i2.3100.
- 28. Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. Wtp for a qaly and health states: More money for severer health states? Cost Eff Resour Alloc. 2013;11:22. https://doi.org/10.1186/1478-7547-11-22.
- Moradi N, Rashidian A, Nosratnejad S, Olyaeemanesh A, Zanganeh M, Zarei L. Willingness to pay for one quality-adjusted life year in iran. Cost Eff Resour Alloc. 2019;17(1):4. https://doi.org/10.1186/s12962-019-0172-9.
- 30. Reckers-Droog V, van Exel J, Brouwer W. Willingness to pay for health-related quality of life gains in relation to disease severity and the age of patients. Value Health. 2021;24(8):1182-92. https://doi.org/10.1016/j.jval.2021.01.012.
- Zillich AJ, Blumenschein K, Johannesson M, Freeman P. Assessment of the relationship between measures of disease severity, quality of life, and willingness to pay in asthma. Pharmacoeconomics. 2002;20(4):257-65. https://doi.org/10.2165/00019053-200220040-00004.
- Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. CA Cancer J Clin. 2018;68(2):153-65. https:// doi.org/10.3322/caac.21443.
- 33. Hoang VM, Pham CP, Vu QM, Ngo TT, Tran DH, Bui D, et al. Household financial burden and poverty impacts of cancer treatment in vietnam. Biomed Res Int. 2017;2017:9350147. https://doi.org/10.1155/2017/9350147.
- 34. ACTION Study Group. Policy and priorities for national cancer control planning in low- and middle-income countries: Lessons from the association of southeast asian nations (asean) costs in oncology prospective cohort study. Eur J Cancer. 2017;74:26-37. https://doi.org/10.1016/j.ejca.2016.12.014.
- 35. Ngan TT, Van Minh H, Donnelly M, O'Neill C. Financial toxicity due to breast cancer treatment in low- and middle-income countries: Evidence from vietnam. Support Care Cancer. 2021;29(11):6325-33. https://doi.org/10.1007/s00520-021-06210-z.
- 36. Hoang Lan N, Laohasiriwong W, Stewart JF, Tung ND, Coyte PC. Cost of treatment for breast cancer in central vietnam. Glob Health Action. 2013;6:18872. https://doi.org/10.3402/gha.v6i0.18872.

- 37. Tafazzoli A, Ramsey SD, Shaul A, Chavan A, Ye W, Kansal AR, et al. The potential value-based price of a multi-cancer early detection genomic blood test to complement current single cancer screening in the USA. Pharmacoeconomics. 2022;40(11):1107-17. https://doi.org/10.1007/s40273-022-01181-3.
- 38. Iino H, Hashiguchi M, Hori S. Estimating the range of incremental cost-effectiveness thresholds for healthcare based on willingness to pay and gdp per capita: A systematic review. PLoS One. 2022;17(4):e0266934. https://doi. org/10.1371/journal.pone.0266934.
- 39. Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: Initial estimates and the need for further research. Value in Health. 2016;19(8):929-35. https://doi.org/https://doi.org/10.1016/j.jval.2016.02.017.
- 40. Phuong NTT, Thang TB, Anh NDQ, Hanh NM, Chau HM, Thanh NT, et al. The distribution of gastrointestinal cancer in two specialized oncology hospitals in hue and da nang cities, 2022. Vietnam Journal of Preventive Medicine. 2024;33(6 Phụ bản):104-10. https://doi.org/10.51403/0868-2836/2023/1407.



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