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Review Article

Estimating Taiwan's QALY league table for catastrophic illnesses: Providing real-world evidence to integrate prevention with treatment for resources allocation

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ABSTRACT

Background/purpose: Curative technologies improve patient's survival and/or quality of life but increase financial burdens. Effective prevention benefits all three. We summarize estimation methods and provide examples of how much money is spent per quality-adjusted life year (QALY) or life year (LY) on treating a catastrophic illness under a lifetime horizon and how many QALYs/LYs and lifetime medical costs (LMC) could be potentially saved by prevention.

Methods: We established cohorts by interlinkages of Taiwan's nation-wide databases including National Health Insurance. We developed methods to estimate lifetime survival functions, which were multiplied with the medical costs and/or quality of life and summed up to estimate LMC, quality-adjusted life expectancy (QALE) and lifetime average cost per QALY/LY for catastrophic illnesses. By comparing with the age-, sex-, and calendar year-matched referents simulated from vital statistics, we obtained the loss-of-QALE and loss-of-life expectancy (LE).

Results: The lifetime cost-effectiveness ratios of ventilator-dependent comatose patients, dialysis, spinal cord injury, major trauma, and cancers were US$ 96,800, 16,200–20,000, 5500–5,900, 3400–3,600, and 2900–11,900 per QALY or LY, respectively. The successful prevention of lung, liver, oral, esophagus, stomach, nasopharynx, or ovary cancer would potentially save US$ 28,000–97,000 and > 10 QALYs; whereas those for end-stage kidney disease, stroke, spinal injury, or major trauma would be US$ 55,000–300,000 and 10–14 QALYs. Loss-of-QALE and loss-of-LE were less confounded indicators for comparing the lifetime health benefits of different technologies estimated from real-world data.

Conclusions: Integration of prevention with treatment for resources allocation seems feasible and would improve equity and efficiency.

1. Introduction

Universal health coverage (UHC) with equal accessibility *ensures that no one* becomes impoverished because of illness and is promoted by the World Health Organization (WHO) [1]. Advancements in medical technologies and multiple uncertainties in healthcare services constantly pose financial threats to the sustainability of the UHC system [2]. To address this challenge [3–5], the conventional paradigm of "pay by volume" is growingly replaced by "pay by value" to improve the efficiency or cost-effectiveness [6–8], which facilitates the implementation of health technology assessment (HTA) [9]. Conventional HTA mainly quantifies the incremental cost-effectiveness ratio (ICER), or cost

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per quality-adjusted life year (QALY) gained, through comparison of two technologies of treatment (and/or diagnosis) for a specific health condition [10], which facilitates the quick adoption of the new technology into the healthcare markets through comparison across different illnesses [11,12], or, on a QALY league table [13,14]. However, while all novel technologies invented to treat a disease would prolong survival and/or improve quality of life (QoL), they generally increase the number of prevalent cases and financial burden. Only effective prevention could possibly reverse such trends [15] and should be integrated into national resource allocation across the whole care cycle, namely, prevention, diagnosis & treatment, and care [5,9]. Though the global burden of diseases has been estimated by the WHO using disability-adjusted life year (DALY) and popularly applied in national policy decisions for prevention [15], the unit of DALY cannot be directly compared with QALY commonly used in HTA and clinical practice and the costs of diversified preventive services still needs to be clarified under a lifetime horizon [16].

Taiwan's National Health Insurance (NHI) is a UHC system implemented since 1995. Advances in medical technologies have increased the survival and prevalent cases of patients for the top five catastrophic illnesses, which has resulted in growing financial burdens of autoimmune disease and cancer up to 7.7 and 5.4 times, respectively, and threatens the sustainability (Fig. 1) [17]. Although Taiwan's NHI stipulates HTA be performed for setting the reimbursement prices of medical technologies [18,19], the current provision does not yet cover preventive services. Using real-world data (RWD), my team developed novel methods [20–23] for estimations of lifetime survival functions, life expectancies (LEs), quality-adjusted life expectancies (QALEs), lifetime costs for cancer of different organ-systems, which were compared with age-, sex-, and calendar year-matched referents to quantify the potential savings of successful prevention for cancer, which is presented as the first lifetime QALY league table for cancer in Taiwan [24,25]. We further demonstrated that cost-effectiveness assessment of cancer screening as a prevention measure is feasible [26–28]. As successful prevention of a cancer or treatment of a heroin user [29], would lead to a completely new life course, we tentatively assumed that total lifetime costs spent for a specific catastrophic illness could be potentially saved by effective prevention.

When QALE/LE, loss of QALE/LE, lifetime medical costs are transparently provided across different catastrophic illnesses and care technologies, all the stakeholders would have equal opportunities to improve health equity and efficiency in resource allocation. We present this mini-review to share the conceptual framework and more extensive empirical examples as evidence of the feasibility of HTA across the care cycle, including prevention.

2. Subjects and methods

This study was commenced after it was approved by the institutional review board of National Cheng Kung University Hospital (NCKUH; IRB numbers B-ER- 104-103 and B-ER-108-416).

3. Conceptual framework for quantifying the health benefits of prevention

The total sum of health benefits resulting from prevention, through reducing or changing the incidence rate, could be multiplied with the population at risk to obtain the expected number of preventable cases. The consequence of an index case could be estimated by multiplying the lifetime survival function with a second function, e.g., quality of life, medical costs, functional disabilities, etc., resulting in quality-adjusted life expectancy, lifetime medical costs, lifetime living with functional disabilities, etc., after occurrence of the event, as summarized in Fig. 2. Then, the health benefits from successful prevention of an index case could be estimated by calculating the potential savings of loss of QALE/LY and lifetime medical costs, which would be the difference between the index case and age, sex, calendar year-matched referents simulated from vital statistics of the general population. The societal impact(s) of productivity loss, additional environmental burdens, etc., could also be estimated if the data were available [8].

4. Empirical examples

We interlinked the Claims Database of Taiwan's NHI, Taiwan Cancer Registry, and Taiwan Mortality Registry to establish the index cohorts with different diseases that would result in premature mortality (Supplementary Table 1). The datasets contained data of the patients' detailed demographics; International Classification of Diseases (9th

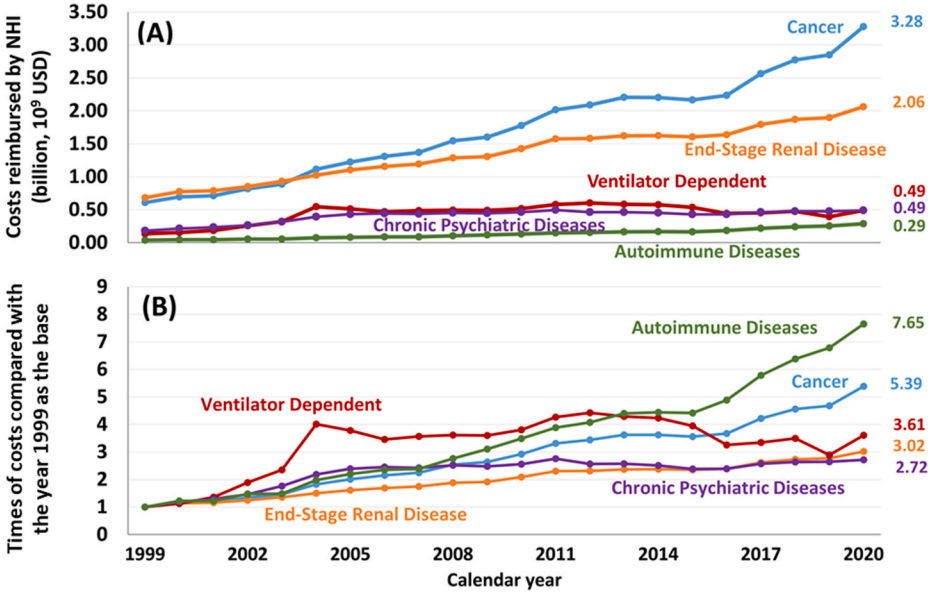

Fig. 1. Trends in medical costs of 5 major catastrophic illnesses over time in Taiwan.
Legend of Fig. 1: The upper panel (A) shows the annual total costs reimbursed by the National Health Insurance (NHI) in billions of USD (adjusted to 2020), while the lower panel (B) shows the relative increase in financial burden using no. of times of the annual cost in 1999 as the base for each illness. (Note: ventilator dependent illness includes all patients who relied on prolonged mechanical ventilation for more than 3 weeks).

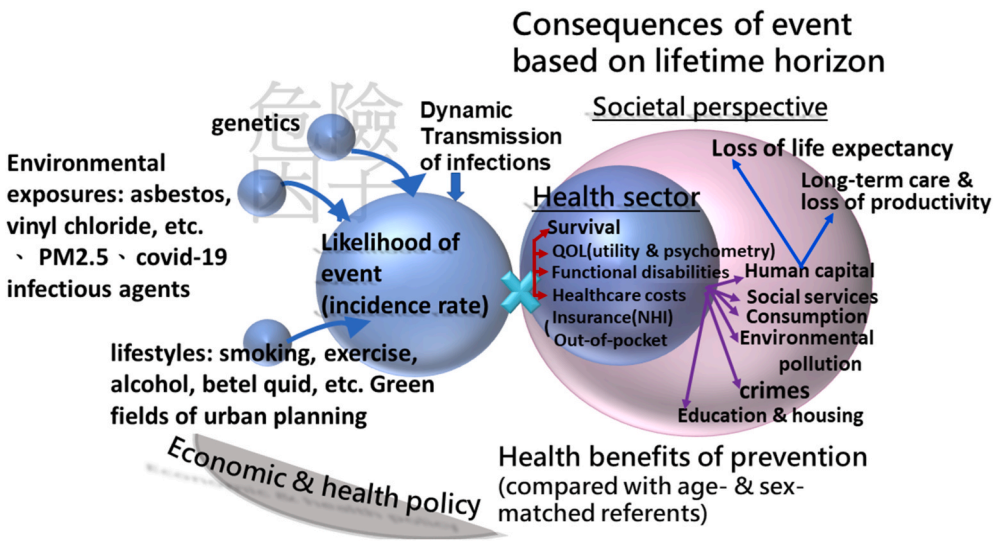

Fig. 2. Consequences of event based on lifetime horizon.
Legend of Fig. 2: The health impact of an event (namely, catastrophic illness) is mainly determined by the likelihood of the event multiplied with lifetime consequence(s) of the event. While the former can be generally quantified by incidence rates through epidemiological studies (bluish cycles on the left side), the latter could usually be quantified by estimating the lifetime survival function multiplied with a second function, e.g., quality of life, medical costs, functional disabilities, etc., resulting in quality-adjusted life expectancy, lifetime medical costs, lifetime living with functional disabilities, etc., after occurrence of the event (the bluish cycle on the right under health sector). One may further estimate societal impact [8] by multiplying survival with employment ratio and/or salary, etc., for productivity indicated in the bigger pink cycle.

edition; ICD-9) and ICD-10 codes; dates of diagnoses; cancer sites and histopathology; and health care expenditure covered by the NHI. The patients' personal information was protected by encrypting their identification numbers. All index diseases included in this study were categorized as catastrophic illnesses, except acute myocardial infarction.

5. Estimation of lifetime survival functions, life expectancy (LE), and loss-of-LE

The survival functions of the index cohorts were estimated by using the Kaplan–Meier method until the end of follow-up. Then, they were extrapolated to lifetime using a rolling extrapolation algorithm, aided by the age-, sex- and calendar year-matched referents simulated from the life tables of National Vital Statistics [22,23,29,30]. Using cancer as an example, we briefly summarized the procedure in three steps. First, we ascertained that every new cancer case in the index cohort was alive or deceased at the end of follow-up. The survival function of the index cohort, denoted as $S(t|index)$, was estimated using the Kaplan-Meier method for $t \le F_S$, where F_S is the maximum follow-up time. Second, we simulated the survival times of the age- and sex-matched referents according to the life table of the same calendar year of diagnosis and established a dataset size of approximately 100,000. Then, we applied the Kaplan–Meier method to estimate the lifetime survival curve for the simulated reference cohort, denoted as $S(t|ref)$. Third, we performed a logit transformation of the relative survival, $W(t) = S(t|index)/\,S(t|ref)$. The logit transformation of W(t) would approximate to a straight line under the assumption that the study cohort has an excessive constant hazard of mortality. We used restricted cubic spline models to fit $\text{logit}(W(t))$ for the observed time period $t = 1, 2, \ldots, F \le F_s$. With the fitted restricted cubic spline model, we extrapolated $\text{logit}(W(t))$ to only one month ahead. The predicted value of the next-month $\text{logit}(W(F+1))$ was accurate for the property of approximate linearity and was treated as an "observation" at time $F+1$. We repeated the above extrapolation procedures month-by-month by fitting a new restricted cubic spline model to the updated period of the same length, dropping the first observation and adding the newly "observed" value to the end. Through repeated rolling-over monthly extrapolation, we estimated the lifetime survival function of the index cohort with the following equation:

$$\widehat{S}(t_{F+k}|index) = S(t_{F+k}|ref) \times \frac{\exp[logit - W(t_{F+k})]}{1 + exp[logit(-W(t_{F+k})]} \text{ for } k = 1, 2, 3, \ldots, L - F.$$

Where, F is the last month before starting extrapolation of the survival function and L is the month when the survival rate of the cancer patients is close to zero (namely, below 0.1%). All the above procedures were performed using the iSQoL2 package which can be freely downloaded at the following website: http://sites.stat.sinica.edu.tw/isql/. The loss-of-LE for each index cohort was obtained by comparing the LE between the index cohort and their corresponding matched referents. The standard errors and 95% confidence intervals of the estimate of LE and loss-of-LE were obtained using bootstrap methods. A detailed description can be found in the supplementary online content using liver cancer as an example [31].

6. Estimation of lifetime medical costs (LMC)

Taiwan's NHI tries to prevent people from becoming financially bankrupt due to any catastrophic illness. Hence, people successfully registered as having a catastrophic illness can be waived from all copayments. To avoid abuse, NHI generally requires two board certified physicians to validate the condition. Patients with malignancies of all organ-systems, all diseases listed in Tables 1 and 2, rare diseases, ventilator-dependent (received more than 3 weeks of mechanical ventilation) are eligible for inclusion in the registry. The charges of inpatient hospitalization, outpatient clinics, emergency services, required laboratory & imaging tests, medicine prescriptions and surgeries are covered comprehensively. We added all the reimbursement costs for every case and calculated the monthly average after diagnosis of the specific illness. The estimated lifetime cost was calculated by adding the product of monthly survival rates and associated mean costs over the lifespan [24,25]. To facilitate comparisons across different calendar years and illnesses, we adjusted all the cost values up to the year 2020. The monthly mean costs beyond the maximum follow-up were estimated by the weighted averages of the mean expenditures of subgroups of patients alive at the month would die within a specific

Table 1
QALY league table (cost per QALY) for treating the disease and lifetime health benefits and costs potentially saved by successful prevention.

	Value of lifetime diagnosis & treatment				Potential lifetime savings from prevention			
	Cost per QALY (x10^3 USD)		QALE (QALY as unit)		Loss-of-QALE (QALY as unit)		Lifetime cost (x10^3 USD)	
Cancer [24,25]	**(Male)**	**(Female)**	**(Male)**	**(Female)**	**(Male)**	**(Female)**	**(Male)**	**(Female)**
Lung	11.5	9.1	2.3 (2.2–2.4)	4.2 (3.9–4.5)	11.9	14.3	26.5 (26.1–27.0)	38.2 (36.6–40.0)
Liver	6.6	6.6	4.3 (4.2–4.5)	4.4 (4.2–4.5)	15.1	13.1	28.5 (27.7–29.2)	28.8 (27.9–29.7)
Oral	5.5	3.9	11 (10.7–11.5)	14.2 (12.8–15.3)	14.6	9.0	60.3 (58.6–62.0)	55.5 (49.6–61.4)
Esophageal	11.9	7.7	2.7 (2.5–2.9)	3.8 (3.1–4.6)	18.1	13.9	32.1 (31.3–32.9)	29.2 (26.2–32.3)
Colorectal	5.0	4.4	10.1 (9.9–10.3)	11.8 (11.5–12.0)	6.3	7.4	50 (49.1–51.0)	52.4 (51.2–53.6)
Stomach	5.6	4.4	5.7 (5.5–5.9)	8.2 (7.6–8.6)	9.1	10.9	31.7 (30.8–32.6)	36.3 (34.4–38.0)
Nasopharyngeal	4.7	4.2	13.0 (12.2–13.8)	15.0 (13.2–17.1)	14.2	16.3	60.5 (56.7–64.4)	63.3 (57.1–69.3)
Bladder	5.5	9.1	9.6 (9.1–10.1)	9.4 (8.8–9.9)	5.0	7.1	52.4 (50.5–54.1)	85.7 (79.6–91.6)
Kidney	5.9	4.7	12.5 (11.1–13.4)	14.6 (11.9–16.3)	7.5	8.5	74.1 (67.5–80.7)	69.3 (59.2–79.3)
Renal pelvis & ureter	8.4	11.2	8.0 (7.4–8.7)	8.7 (8.0–9.6)	7.8	7.4	66.8 (62.4–71.3)	97.3 (89.6–104.8)
Prostate	5.8	–	8.6 (8.4–8.8)	–	2.7	–	50.3 (49.0–51.4)	–
Breast	–	4.0	–	21.9 (21.3–22.4)	–	7.2	–	86.5 (83.3–89.6)
Cervix	–	2.9	–	19.8 (19.4–20.2)	–	6.0	–	56.4 (54.7–58.1)
Ovary	–	3.6	–	18.5 (17.7–19.3)	–	11.9	–	66.7 (62.8–70.6)
Major illness								
Stroke [23,36]	**(IS)**	**(ICH)**	**(IS)**	**(ICH)**	**(IS)**	**(ICH)**	**(IS)**	**(ICH)**
	5.5	6.6	9.2 (8.6–9.8)	7.6 (6.0–9.2)	7.8	14.5	50.6 (49.9–51.3)	50.3 (48.7–51.8)
End-stage renal disease [37,38]	**(HD)**	**(PD)**	**(HD)**	**(PD)**	**(HD)**	**(PD)**	**(HD)**	**(PD)**
	20.0	16.2	16.4 (15.5–17.3)	17.4 (16.9–17.9)	12.6	8.8	328.1 (319.6–336.7)	282.0 (275.4–288.8)
Prolonged mechanical ventilation [39]	**(PC)**	**(COMA)**	**(PC)**	**(COMA)**	(PC)	(COMA)	**(PC)**	**(COMA)**
	48.8	96.8	0.93 (0.60–1.26)	0.47 (0.29–0.65)	–	–	45.4	45.4

Abbreviations: IS- ischemic stroke; ICH- intracerebral haemorrhage; HD-hemodialysis, PD-peritoneal dialysis; PC: partial cognition, COMA: comatose.

Table 2
QALY/LY league table (cost per life year) for treating the disease and lifetime health benefits and costs potentially saved by successful prevention.

Catastrophic illness	Value of lifetime treatment				Potential lifetime savings from prevention			
	Cost per life year (x10^3 USD)		LE (life expectancy) (life year as unit)		Loss-of-LE (life year as unit)		Lifetime cost (x10^3 USD)	
	(Male)	**(Female)**	**(Male)**	**(Female)**	**(Male)**	**(Female)**	**(Male)**	**(Female)**
Spinal cord injuries [40]	5.9	5.5	17.5 (16.1–19.6)	17.7 (15.1–22.4)	13.0 (10.9–14.5)	14.3 (9.4–16.9)	102.6 (96.1–109.8)	97.7 (85.4–105.1)
Major Trauma [41]	3.6	3.4	16.4 (15.4–17.4)	16.2 (15.2–17.2)	13.6 (12.6–14.6)	13.8 (12.8–14.8)	59.6	54.3
Rheumatoid arthritis [42]	3.6	3.8	21.6	23.4	4.1	9.7	78.3	90.0
Schizophrenia [43]	1.9	1.7	31.4 (31.3–31.5)	35.8 (35.7–35.9)	9.7 (9.6–9.8)	7.6 (7.5–7.7)	59.4 (55.7–63.0)	61.4 (57.7–65.0)
Alzheimer disease [44]	**(Early)**	**(Late)**	**(Early)**	**(Late)**	**(Early)**	**(Late)**	**(Early)**	**(Late)**
	3.5	4.8	13.8 (12.0–15.6)	9 (8.8–9.2)	8.7 (6.7–10.7)	1.7 (1.5–1.9)	48.8 (45.7–51.9)	43.4 (42.4–44.5)
Myocardial infarction [30]	**(PCI)**	**(non-PCI)**	**(PCI)**	**(non-PCI)**	**(PCI)**	**(non-PCI)**	**(PCI)**	**(non-PCI)**
	3.7	4.3	16.5 (15.5–17.5)	12.7 (12.1–13.3)	3.6 (2.6–4.6)	5.2 (4.6–5.8)	61.4	55.2

Abbreviations: QALY- quality-adjusted life year; LY- life year; LE-life expectancy; Early-early onset; Late-late onset; PCI- percutaneous coronary intervention.

number of months and those who would live beyond, where the mean expenditures of a subgroup was decided according to the observed costs in the patients' last months prior to death and the corresponding weight was the mortality hazard of the subgroup at that month which can be estimated from the extrapolated hazard of mortality [23]. The estimates of lifetime costs were also calculated using the iSQoL2 package [32].

7. Estimation of quality-adjusted life expectancy (QALE), and loss-of-QALE

All patients with cancer who visited the outpatient clinic of NCKUH were invited to fill out the questionnaires of EuroQol-5dimentions (EQ-5D) [33] and World Health Organization Quality-of-Life-Brief (WHO-QOL-BREF) [34]. Informed consent was obtained. A trained assistant responded to the patients' questions. To conduct longitudinal analysis of the dynamic changes in QoL, we collected repeated measurements if the previous measurement was taken more than two weeks ago. The questionnaires were administered with a computerized tablet or cellular phone inside NCKUH depending on the condition of the patients. A total of 19,055 patients were enrolled with 57,294 repeated measurements obtained between May 2011 and September 2022. The EQ-5D questionnaire is a generic and preference-based tool and can be converted into a utility value [33] The mean QoL across time was calculated using the kernel smoothing method [20], and the mean utility value at each month was multiplied by the corresponding survival rate for the calculation of the quality-adjusted survival function. The area under the curve would be the QALE with the unit of QALY [21,22]. The loss-of-QALE was calculated by subtracting the QALE of patients with cancer from the QALE of the age-, gender-, and calendar year-matched referents simulated from the vital statistics. The EQ-5D utility values of the general population were derived from our national survey [35].

8. Estimation of the lifetime cost-effectiveness ratio for each index disease

The cost-effectiveness ratio of every index disease is the average total lifetime cost of the index disease divided by the QALE of the disease. To synchronize the values with the annual discount from the estimation of lifetime costs, we adopted a 3% annual discount rate in the estimation of LE and QALE when calculating the ratio [12,19].

9. Results

Table 1 summarizes the estimated average lifetime cost per QALY, QALE, under Taiwan's NHI and potential savings from the successful prevention of a case of 14 cancers [24,25], stroke [23,36], end-stage renal disease [37,38], and prolonged mechanical ventilation (PMV) [39]. A similar LY league table for other catastrophic illnesses was also summarized for the following major illnesses: spinal cord injuries [40], major trauma [41], rheumatoid arthritis [42], and schizophrenia [43], Alzheimer's disease [44], and myocardial infarction [30]. Given that the estimated loss of QALE/LE were adjusted for different distributions of age, sex, and calendar year of medical technology, we provided information about potential lifetime savings from the successful prevention of these illnesses at different time periods and with different technologies. For instance, when the occurrence of liver, lung, esophagus, or nasopharynx cancer was successfully prevented, more than 10 QALYs and more than US$21,000 per case would be saved for both genders. Moreover, the lifetime cost per QALY/LY of different illnesses in Tables 1 and 2 provides stakeholders with a comparison of the average burden of caring for different illnesses over a lifetime horizon. For example, PMV would be the most expensive technology, costing approximately $US96,800 per QALY for patients with various underlying diseases [39]. The QALY league table is also depicted in Fig. 3 showing the slope of the lifetime average cost per QALY, in which the assumed threshold once recommended by the WHO, or, 1–3 GDP per QALY is also illustrated, and the slope for PMV was the steepest among all the illnesses [11].

10. Discussion

The validity of our findings can be corroborated by the following arguments: First, given that all the catastrophic illnesses listed in Tables 1 and 2 are eligible to be waived from all copayments in Taiwan's NHI (except myocardial infarction), the diagnosis of each patient must be validated by two specialists to prevent any misuse. In this study, patients with myocardial infarction were recruited from hospitalization records [30]. Thus, the accuracy of diagnosis is assured and the incentive of waiving all copayments guarantees the comprehensiveness of the nationwide data in reimbursement costs and case recruitment. Second, we have developed a novel rolling-over algorithm for the extrapolation of survival functions of the index cohorts to lifetime. In addition to considering the age-, sex-, and calendar year-matched referents to obtain the relative survival [23–25,29,30,45], we constructed a restricted cubic spline model to extrapolate the survival rate one month at a time. By repeatedly adopting the newly estimated monthly survival rate, we successfully estimated the lifetime survival function without the strict assumption of the constant excess hazard after the end of follow-up [22,23,45]. We adopted a cohort lifetable for referents to minimize underestimation of LE and loss-of-LE [46]. Moreover, we validated each estimate by applying the same extrapolation method to the established cohorts in the first half of the observed period to the end of follow-up and then compared them with the gold standard of the Kaplan–Meier's estimate calculated from actual follow-up. The relative biases were usually less than 1%–5% and not higher than 10% [24,26–28,30,40–43]. As most cohorts were followed for longer than 10–15 years or close to their life expectancy, the accuracy of extrapolations was acceptable. Third, all oncology patients who visited the outpatient department at NCKUH were invited to provide QoL data with repeated measurements from 2011 to 2022. A previous validation study corroborated the representativeness and comparability of our sample across different cancer types [47]. Cross-sectional QoL data on patients with stroke [36] and ESRD [37] were collected from National Taiwan University Hospital and NCKUH, respectively. Therefore, we were able to capture the dynamic changes in the patients' QoL at each time point to be weighted by the corresponding survival probability for quantifying the QALE [20,48,49]. Such estimations would be more accurate than simply multiplying the LE of the index cohort with the average QoL utility. We thus tentatively conclude that our estimated QALE, loss-of-QALE, lifetime medical costs and lifetime average cost-per-QALY would be relatively accurate and acceptable for policy decision-making.

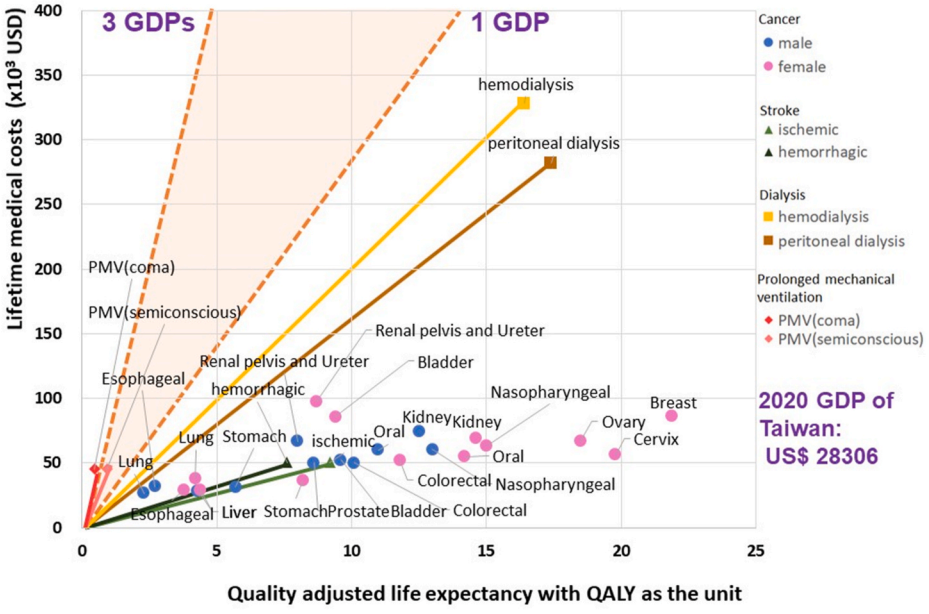

Fig. 3. Generalized cost-effectiveness analysis across different major illnesses under a lifetime horizon
Legend of Fig. 3: Fourteen different organ-system cancers are depicted as reddish (female) and bluish (male) round dots according to their lifetime costs and QALE (quality adjusted life expectancy). Comatose patients receiving prolonged mechanical ventilation (PMV, or, ventilator-dependent), dialysis, and those with stroke are also illustrated with diamond, rectangular, and triangular dots, respectively, along with straight lines connected to the origin of coordinates to indicate the steepness of slopes. The higher the slope, the higher the cost-per-QALY. The potential threshold of 1–3 GDP (gross domestic product) per QALY once recommended by the WHO is also highlighted in light orange for comparison.

11. Lifetime average cost per QALY: an indicator for generalized cost-effectiveness analysis [11,12]

We estimated the lifetime survival function for the index cohorts, which served as the weights for the monthly mean costs [23] and average utility value [20] at each time point to be summed up for LMC and QALE, respectively. After adopting a 3% discount rate for costs and QALE, we obtained the "cost per QALY/LY" as a comparator [8,12,50] for GCEA [11,12] under a lifetime horizon. Fig. 3 illustrates a generalized comparison of the slope of lifetime cost divided by QALE across different illnesses, indicating that PMV service [39] is the least cost-effective. The findings provide evidence for the modification of regulations allowing the extubation of ventilators for comatose patients under PMV near the end of life in Taiwan [51] and reverses the tendency for increasing reimbursement in 2013 (Fig. 1).

Although QALY is the same across different illnesses, it cannot simultaneously indicate the marginal value for the QALY gained on the specific illness due to different QALEs among illnesses (Tables 1 and 2) [52]. Thus, the ICER calculated by conventional HTA would assure the efficiency of a UHC system, if a cost-effectiveness threshold is established and followed [53], but it cannot assure the fairness in distribution. We provide stakeholders with the estimated QALE/LE alongside each illness in the QALY/LY tables, which would make the total expected costs for a specific illness more transparent. Moreover, the provision of loss-of-QALE/LE and LMC would inform stakeholders the missed opportunities and resources already spent for each catastrophic illness (Tables 1 and 2). The additional information would facilitate a fairer allocation of resources across different illnesses and technologies, and improve the equity and sustainability of a UHC system.

12. Loss-of-QALE and loss of LE as indicators in the comparison of RWE to reduce potential confounding

In a randomized controlled trial, the survival functions of two or more healthcare services are usually compared through Kaplan–Meier estimators. Whereas in observational studies, one often applied propensity score matching and/or inverse probability treatment weighting to adjust the effects of all measured confounding variables [54]. However, in decisions regarding national resource allocation involving multiple technologies and illnesses, potential confounding of different distributions of age, sex, and calendar year of medical technology of different cohorts collected from long-term RWD are the main focus. We proposed to compare the loss of LE or loss-of-QALE, which is a measure of the lifetime loss of an index cohort compared with the age-, sex-, and diagnosis year-matched general population which could be compared across multiple technologies and illnesses with reduced confounding effects from different baseline characteristics. As a corollary, difference-in-differences (DID) can be obtained as an indicator for comparing the effectiveness between two technologies. For instance, while comparing the effectiveness of screening lung cancer with low-dose computed tomography (LDCT) and regular chest film, we found that the ICER was slightly lower by comparison of loss-of-QALE [26] in contrast to that of comparing two QALEs. As shown in Fig. 4, the average ages of patients with stages I and IV adenocarcinoma of the lung were 63.5 and 66.3 years, respectively. The difference in LE between the two technologies showed a health benefit of 11.5 (13.5 − 2) years for LDCT, which would be reduced to 9.3 (16.8 − 7.5) years by comparing the loss of LE to adjust for early detection at a younger age [55]. The DID could also be applied in the comparison of treatment effectiveness, such as opioid agonist treatment (OAT) in heroin users [29] and possibly rare diseases [56].

13. Limitations

This study has the following limitations: First, since our QoL utility values were mostly collected in an outpatient setting, the patients in our study tended to be younger and had better performances. Therefore, the QALE might have been overestimated, and the loss of QALE may have been underestimated for patients with cancer. Second, the reference groups simulated from vital statistics were only matched for age-, gender-, and calendar year to adjust for demographic characteristics and technology advancement. Future studies may consider establishing reference cohorts matched for major comorbidities and relevant determinants to further improve the validity of comparison. Third, our

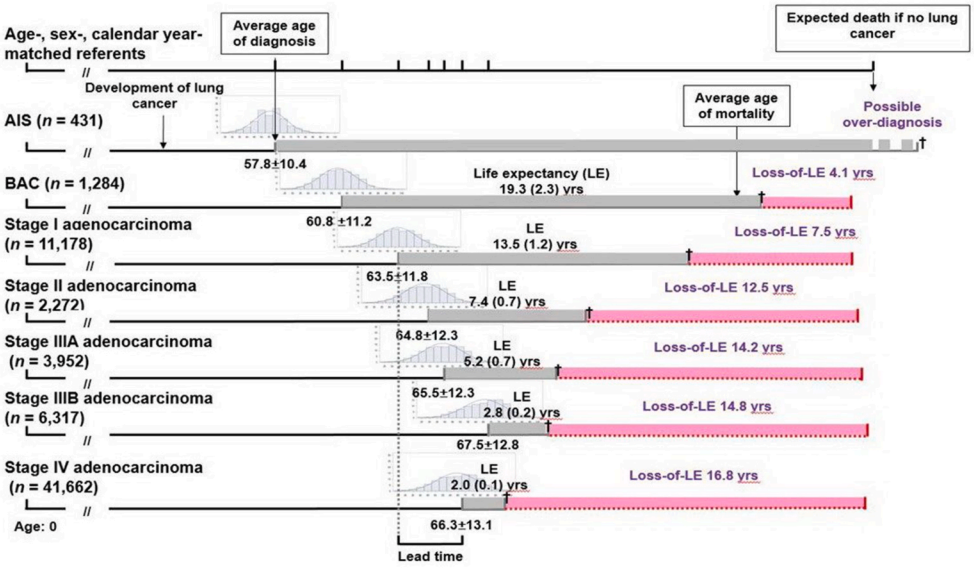

Fig. 4. Lead time bias adjusted by comparison of loss-of-life expectancy (LE) using real world evidence of lung adenocarcinoma from Taiwan Cancer Registry 2002–2015 as an example.

Legend of Fig. 4: Lead time bias developed when patients with lung adenocarcinoma diagnosed at an earlier stage (I) are generally younger than those diagnosed at late stage (IV), 63.5 ± 11.8 versus 66.3± 13.1 years old, respectively. The former's LE was 13.6, while that of the latter was 2.0 with an apparent difference of 11.6 years of longer survival for stage I compared with stage IV. However, if we compared their loss-of-LE's, which was the difference of their LE with corresponding age-, sex-, and calendar year-matched referents, then the difference-in-differences would become 9.3 (=16.8–7.5), implying a lead time bias of 2.3 (=11.6–9.3) was adjusted. (AIS: adenocarcinoma in situ; BAC: bronchioloalveolar carcinoma).

methods relied on the availability of RWD with long-term follow-up (usually more than 5–10 years), which implied the need to extrapolate the survival function of the index cohort to lifetime under a constant hazard assumption [23]. Namely, a cohort with a specific illness would share the same mortality rate as the age-, sex-, and calendar year-matched referents of the general population, except the illness of interest. Although the assumption would generally hold for major catastrophic illnesses causing premature mortality, such as cancer [24,45], it might not stand firm for acute myocardial infarction that can be saved by re-vascularization through early coronary intervention [30]. Thus, we developed a rolling-over algorithm and repeatedly constructed restricted cubic spline models to accommodate minor violation of the above assumption [23,30]. Moreover, we further validated our estimation by using the first half of the observed period to extrapolate to the end of follow-up and to test if the relative biases of the extrapolation were small. In general, a long period of follow-up after the initial treatment (or, a censored rate lower than 75–80%) would be helpful for accurate prediction. Future refinement and sensitivity analysis of different extrapolation methods based on survival data over a shorter period is warranted to extend the applicability and coverage of diseases [45,57]. Fourth, although the LMC summed from reimbursement data were attributed to the specific catastrophic illness and used for HTA of cancer screenings [26–28], the successful prevention of a major cardiovascular (CV) event such as stroke or myocardial infarction may simultaneously reduce the risks of most other CV events. For example, control of 5 or 8 modifiable risk factors [58,59] would simultaneously postpone the development of diabetes, chronic renal failure, cancer, and dementia, etc. Thus, different ways of summing potentially saved benefits and costs for different prevention strategies should be developed, as outlined in Fig. 2. Finally, this study does not yet include out-of-pocket payments nor costs considered from the societal perspective [8], such as productivity loss [60,61], functional disabilities requiring social services [62–64], and impacts of environmental pollution and climate change [65], which should be covered comprehensively in future studies.

14. Conclusion

By analyzing RWD, we were able to quantify QALE/LE and lifetime average cost-per-QALY/LY, listed in league tables, plus LMC and loss-of-QALE/LE that could potentially be saved from successful prevention of a catastrophic illness. The novel methods and evidence from RWD would not only facilitate fair resource allocation across different illnesses but also integrate HTA across the whole care cycle, including prevention, diagnosis, treatment, and care [5] and accelerate the modern healthcare reform of pay-by-value or better outcome per dollar spent.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) did not use any AI or AI-assisted technologies in the writing process.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jung-Der Wang reports was provided by National Science and Technology Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2024.05.011.

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