Socio-economic costs of rare diseases and the risk of financial hardship: a cross-sectional study

Claudia C. Y. Chung,[a] Nicole Y. T. Ng,[a] Yvette N. C. Ng,[b] Adrian C. Y. Lui,[b] Jasmine L. F. Fung,[a] Marcus C. Y. Chan,[a] Wilfred H. S. Wong,[a] So Lun Lee,[a] Martin Knapp,[c,*] and Brian H. Y. Chung[a,**]

[a]Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[b]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
[c]Department of Health Policy, Care Policy and Evaluation Centre, London School of Economics and Political Science, London, United Kingdom

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Summary

Background To achieve universal healthcare coverage (UHC), the rare disease (RD) population must also receive quality healthcare without financial hardship. This study evaluates the impact of RDs in Hong Kong (HK) by estimating cost from a societal perspective and investigating related risk of financial hardship.

Methods A total of 284 RD patients and caregivers covering 106 RDs were recruited through HK's largest RD patient group, Rare Disease Hong Kong, in 2020. Resource use data were collected using the Client Service Receipt Inventory for Rare disease population (CSRI-Ra). Costs were estimated using a prevalence-based, bottom-up approach. Risk of financial hardship was estimated using catastrophic health expenditure (CHE) and impoverishing health expenditure (IHE) indicators. Multivariate regression was performed to identify potential determinants.

Findings Annual total RD costs in HK were estimated at HK$484,256/patient (United States (US) $62,084). Direct non-healthcare cost (HK$193,555/US$24,814) was the highest cost type, followed by direct healthcare (HK$187,166/US$23,995), and indirect (HK$103,535/US$13,273) costs. CHE at the 10% threshold was estimated at 36.3% and IHE at the $3.1 poverty line was 8.8%, both significantly higher than global estimates. Pediatric patients reported higher costs than adult patients ($p < 0.001$). Longer years since genetic diagnosis was the only factor significantly associated with both total costs ($p = 0.026$) and CHE ($p = 0.003$).

Interpretation This study serves as the first in the Asia Pacific region to simultaneously assess the societal costs and financial hardship related to RDs and highlights the importance of an early genetic diagnosis. These results contribute to existing evidence on the globally ubiquitous high costs of RDs, warranting collaboration between different stakeholders to include RD population in UHC planning.

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Keywords: Rare disease; Societal cost; Socio-economic burden

Introduction

As defined by the World Health Organization (WHO), rare diseases (RDs) are conditions that affect less than 5 in 10,000 within the European population.[1] The rarity of each of the 6000–8000 known RDs limits medical knowledge, causing long diagnostic odyssey, lifelong disabilities and costly treatments.[2] In 2019, Rare Diseases International released a position paper

Abbreviations: WHO, World Health Organization; RD(s), rare disease(s); UHC, universal healthcare coverage; SDGs, sustainable development goals; UN, United Nations; OOP, out-of-pocket; CHE, catastrophic health expenditure; IHE, impoverishing health expenditure; HK, Hong Kong; US, United States; CSRI-Ra, Client Service Receipt Inventory for RAre disease population; CI, confidence interval

*Corresponding author. Care Policy and Evaluation Centre, Department of Health Policy, London School of Economics and Political Science, Houghton Street, London, WC2A 2AE, United Kingdom.
**Corresponding author. Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, The University of Hong Kong, 1/F New Clinical Building, Queen Mary Hospital, Hong Kong SAR, China.
E-mail addresses: M.Knapp@lse.ac.uk (M. Knapp), bhychung@hku.hk (B.H.Y. Chung).

Research in context

Evidence before this study

The nature of rare diseases brings about many uncertainties, including its associated costs. There is increasing evidence that costs of diseases not only arise from the utilization of healthcare but also from non-healthcare or indirect factors, ultimately causing financial hardship. Therefore, identifying the areas in which the socio-economic burden falls on is important for effective resource planning and allocation. Considering rare diseases as a whole enables within and between disease group comparisons of resource utilization and facilitates the tracking of overall disease burden over time. We searched for relevant studies evaluating the cost of rare diseases from a societal perspective on the PubMed database from inception to December 21, 2021. The search terms "rare diseases" and "financial hardship" or "socio-economic" or "catastrophic health expenditure" or "impoverishing health expenditure" and "cost of illness" were used. Majority of the studies only considered costs of one specific rare disease or costs only from a health system perspective. Only one collection of studies in Europe considered the societal costs of 10 selected rare diseases. An additional study by a private company in the United States was retrieved by google search using the term "burden of rare diseases". Only two studies attempted to estimate catastrophic health expenditure (CHE) or impoverishing health expenditure (IHE) in the rare disease population. We found no existing literature simultaneously evaluating both cost and financial hardship indicators in the same cohort.

Added value of this study

In the first of such studies within the Asia Pacific region, we simultaneously determined the overall cost and risk of financial hardship using CHE and IHE indicators within the same cohort, revealing the true socioeconomic burden of rare diseases in Hong Kong. We report alarmingly high costs and levels of financial hardship even in the context of Hong Kong's progressive health financing structures, suggestive of the inherent risk of financial hardship in the rare disease population at a global scale. Similar to previous studies, direct non-healthcare and indirect costs accounted for a larger proportion of the total burden than direct healthcare costs. We highlight that the rare disease population is often forgotten in society. Stigmatisation and exclusion of the rare disease population in the workplace, and in healthcare and policy planning remain prevalent. These contribute to productivity loss and exclude the rare disease population from necessary social security programmes. Importantly, an early genetic diagnosis was found to be associated with a reduction in both costs and incidence of financial hardship. When corroborating evidence from other studies, socio-economic costs of rare diseases were found to be consistently higher than other common diseases. These findings not only extend the data on cost of rare diseases to the Asia Pacific region, but also highlight potential drivers of the burden of rare diseases worldwide.

Implications of all the available evidence

The distribution of burden of rare disease across direct healthcare, direct non-healthcare, and indirect costs reflects the challenges in working towards universal health coverage for the rare disease population. In efforts to reduce indirect costs, public education is crucial for the recognition of rare conditions and to facilitate integration of the rare disease population into society. Disproportionately high risk of financial hardship calls for improved coordination of care and specific cost sharing policies and legislations that are tailored to the rare disease population. Importantly, in identifying longer years since diagnosis as a key driver of cost, we highlight the need for more research to expand medical knowledge and work towards improving the diagnostic odyssey of rare diseases. Developments within this area, such as the Hong Kong Genome Project and the 100,000 Genomes Project in the United Kingdom, should be prioritised. Rare diseases must be managed differently to other common diseases. The necessary interventions require global collaboration and sharing of information between various stakeholders through international networks such as 'Rare Disease International', and continuous monitoring of the rare disease burden through similar studies.

emphasizing the need for Universal healthcare coverage (UHC) policies to account for RDs.[3] UHC is one of the Sustainable Development Goals (SDGs) laid out by Member States of the United Nations (UN) in 2015[4] and shares common goals with RD movements to provide quality and effective healthcare to all without the risk of financial burden on patients of families.[5] The UN's political declaration on UHC has since recognized the RD population as a marginalized group that should be considered during healthcare planning, arguing that UHC "shall never be fully attained nor realized if persons living with RDs are left behind and their needs left unmet".[3]

Given the low prevalence of individual RDs, it is necessary to quantify the true impacts of RDs as a collective disease. Currently, existing studies investigating RDs as a collective group have only quantified direct medical costs from a health system perspective.[6–8] Consequently, the estimations do not factor in out-of-pocket (OOP) expenditure. OOP health expenditures are additional healthcare costs not covered by the health system but paid by patients themselves or their families and could potentially cause patients to choose between healthcare and other necessities. This risk of financial hardship can be effectively measured using two indicators. Catastrophic health expenditure (CHE) is an

official indicator for monitoring financial protection for UHC among the SDGs (indicator 3.8.2). It identifies households with OOP health expenditure exceeding available resources.[9] Impoverishing health expenditure (IHE) identifies households pushed into poverty due to OOP health expenditure.[10]

In fact, the economic impacts of RDs go beyond the patient and healthcare-associated costs. The direct non-healthcare and indirect costs of RDs must therefore also be considered for a comprehensive evaluation of the socio-economic impact of RDs. This is particularly important in this context, as RDs are often chronically debilitating, requiring lifelong caring by hired and paid formal caregivers, or informal caregivers, who are typically family members or friends providing non-professional and unpaid care and support. Therefore, to estimate the true socio-economic impact of RDs, costs from various levels in the society beyond the healthcare system perspective must also be considered. Simultaneous evaluation of the socio-economic costs from various perspectives and indicators of financial hardship provides an overview of the impacts of RD at a given period in a specific jurisdiction from the perspectives of different stakeholders.[11] Policies and systems currently in place can therefore be evaluated in terms of their ability to address the socio-economic consequences of RDs. A holistic evaluation is necessary to highlight service and resource areas that should be prioritized to aid effective healthcare decision-making under resource and budget constraints, acting as a key to achieving UHC.[12]

Societal costs and risk of financial hardship have yet to be simultaneously evaluated within a single RD population. Previous studies of societal cost of RDs report higher direct non-healthcare and indirect costs than direct healthcare costs,[13,14] while CHE has only been investigated in one heterogenous RD cohort.[15] These studies are limited to jurisdictions in Europe and the United States, and the findings may not be generalizable to other populations. Consequently, there is a need to investigate and identify drivers of the burden of RDs as a collective disease group to encompass its heterogeneity and differential impact in other jurisdictions, namely in the Asia Pacific region.[16]

Among the 7.5 million population in Hong Kong (HK), one in 67 individuals are living with one or more RDs, representing 1.5% of the population.[8] In 2015–2016, the inpatient healthcare cost of RDs was estimated to be HK$1,594,339,530 (i.e. United States (US) $204,402,504), accounting for 4.3% of all inpatient costs in 2015–2016.[8] However, other direct healthcare costs, direct non-healthcare costs, and indirect costs, have yet to be quantitatively evaluated. In an effort to fill the evidence gap in the Asia Pacific region, this study sought to comprehensively evaluate the socio-economic impact of RDs in HK by i) estimating the cost of RDs from a societal perspective, ii) investigating patient's OOP health expenditure as a measure of financial hardship using the CHE and IHE indicators, and iii) identifying potential factors that are associated with the cost of RDs and the incidence of CHE and IHE.

Methods

Study design and participants

This cross-sectional study was conducted between April and August 2020 in HK. RD patients or caregivers of RD patients were recruited through Rare Disease Hong Kong, the first and largest RD patient alliance in HK, and their affiliated patient groups. Patients or caregivers who were not members of any patient groups were recruited via online social media platforms including Facebook, Instagram, and WhatsApp platforms of patient support groups.

All eligible participants meeting inclusion criteria were included in data analysis: i) patients with RDs who could understand and self-complete the Client Service Receipt Inventory for Rare disease population (CSRI-Ra); ii) caregivers of patients with RDs who were unable to complete the CSRI-Ra themselves, including but not limited to patients who were physically or cognitively incapable of self-reporting. All patients and caregivers self-reported their RD diagnosis as determined clinically or molecularly. All reported RDs were reviewed and categorized into one of the 22 disease categories according to the 10th version of the International Classification of Diseases and Related Health Problems (ICD-10).[8] Participants reporting "undiagnosed disease" or diseases that were "not rare" according to WHO definition were excluded from the study. The full inclusion and exclusion criteria are included in Supplementary information 1.

All patients and caregivers were informed of the study's objectives and data confidentiality standards and were recruited on a strictly voluntary basis. Informed consent was obtained from all participants. Ethics approval was granted by the Institutional Review Board, the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 19-609).

Data source

The validated CSRI-Ra,[17] is available in both self-complete and proxy-complete versions and in both English and Traditional Chinese. It was used to collect data in five main areas, namely background characteristics, household and caregiver support, healthcare service and resource utilization, community support, and education and employment.

Cost estimates

A prevalence-based method with bottom-up approach was used to quantify service and resource utilization from a societal perspective. Service and resource use data over a six-month period were collected retrospectively

using the CSRI-Ra.[17] These data were extrapolated to the entire year by multiplying by two to allow the estimation of resource utilization per year per patient.

Service and resource use attributed to RDs were valued by their unit costs, reflecting long-run marginal opportunity costs. Unit costs were obtained from publicly available sources and internal hospital systems and set at 2019/20 prices (Supplementary Table S1). Unit costs not available in the year of 2019/20 were adjusted for inflation using the gross domestic product implicit price deflator to uprate the cost to 2019/20 prices in HK. All costs were reported in HK dollars, which had an exchange rate of 7.8 per US dollar at time of analysis (November 2021).

Costs were categorized into direct healthcare costs, direct non-healthcare costs and indirect costs. No discounting of costs was applied in the analyses as data collected for cost estimation was evaluated over a period of one year.

Direct healthcare costs

Direct healthcare costs were derived from healthcare service and resource utilization, and consisted of health services (inpatient days, outpatient visits, accident and emergency visits, day care attendances, allied health visits, surgeries/procedures), medications, medical resources and consumables, and community medical services (residential/community nursing and allied health services, alternative medicine). To derive the annual cost per patient, unit costs were multiplied by the respective number of units utilized (Supplementary Table S1).

For medications, all drugs reported by the patient/caregiver were cross-checked with the HK Hospital Authority Drug Formulary to check whether they are available under the Hospital Authority and to obtain their drug category if so. Details of the Hospital Authority drug categories are included in Supplementary information 2. Cost of medications in this analysis only included drugs categorized as "Self-financed Items with safety net" or "Self-financed Items without safety net" under the Hospital Authority Drug Formulary, unregistered drugs provided to named patients only, and drugs that are not available under the Hospital Authority (Supplementary information 2). "General" and "Special" drugs covered by the Hospital Authority were included in the unit cost of inpatient days and outpatient visits under Hospital Authority and are not estimated separately to avoid double-counting.

Cost of medications was calculated by determining the unit cost of each drug, multiplied by the dosage, frequency, and duration of use. Additional details are in Supplementary information 2.

Direct non-healthcare costs

Direct non-healthcare costs were quantified by aggregating six items: professional care, informal care, special education and employment services, residential or foster care placements, home modification, and transportation.

Professional care refers to formal care provided by a paid caregiver (e.g. domestic helper, hourly-paid home care worker, escort care worker, etc.). Cost of professional care by domestic helper(s) was valued using national monthly wage for a foreign domestic helper (standard monthly wage of HK$4630 in 2021); and for all other paid caregivers, cost of professional care was estimated by weighing the time spent in care (number of care hours) by the national mean hourly wage for a home helper (Supplementary Table S1).[18] Cost of informal care by unpaid caregiver(s) was valued by the replacement cost method (proxy good method) to value the time spent in care, assuming that a professional caregiver would have been hired instead if the informal caregiver was not available. Conservatively, the maximum number of caring hours per unpaid caregiver was censored to be 16 h per day when the reported time of care exceeded this figure. The national mean hourly wage of a home helper was used to estimate the cost of informal care support.

Special education programs in mainstream schools and special education in aided special schools were valued using the average unit costs per place for the academic year, specific for the school type according to the HK Education Bureau. Special training services were estimated using the average unit cost per month provided by the HK Social Welfare Department and Vocational Training Council for a one-year period. Extra visits to professionals in school were valued using the national unit cost per minute of each professional. To avoid double-counting that has potentially been included in the unit cost per place in special schools, cost of extra visits to school professionals were only estimated among patients attending mainstream schools. RD patients living in residential or foster care placements were valued by the unit cost per month according to the HK Social Welfare Department. Unit costs details are included in Supplementary Table S1; specifics of the school types and special services included are in Supplementary information 3.

Modifications made at home to assist the patient was valued at their unit cost. Annual cost was determined by dividing the unit cost by the expected lifetime years of the equipment/resource. Average monthly expenditure on transportation was collected from the CSRI-Ra and extrapolated to one year.

Indirect costs

Indirect cost was estimated through patient's and informal caregiver's labor productivity losses, and the utilization of health services by family member(s) due to the patient's RD condition. Productivity losses were valued using the human capital approach, which converts time away from work into monetary units based on wage levels. The median monthly gross wage of a worker in HK (HK$18,400/month) was used as a proxy to estimate annual labor productivity losses for the year 2020.

Details on handling of missing data for all cost types are in Supplementary information 4.

Out-of-pocket health expenditure as a measure of financial hardship

Monthly OOP health expenditure and annual household income, including patient's income, caregiver's income, social security support and governmental allowances (Supplementary Table S2) received by individuals from the same household, were collected via the CSRI-Ra for each patient. Total annual household income for each patient was estimated by summing patient's income, caregiver's income, and social security support and governmental allowances received by the patient or any family members from the same household. OOP health expenditure includes any self-financed health services and resources that are not covered by the Hospital Authority. Details on handling missing OOP expenditure data are in Supplementary information 4.

To measure the incidence of financial hardship caused by OOP health expenditure, the CHE indicator and the IHE indicator were used. The CHE was used to identify households for whom their OOP health expenditure was "catastrophically" large relative to available resources. Three CHE thresholds were used, defined as OOP health expenditure greater than 10% and 25% (official SDG thresholds)[9] and 40% (proposed by WHO) of total household income.[19] Individuals with OOP expenditure exceeding these thresholds were recorded to experience CHE. The IHE was used to identify households who were impoverished by OOP health expenditure, with their household income being above the poverty line prior to OOP spending on healthcare, but below the poverty line afterwards. The $1.9 per day poverty line (extreme poverty line) and the $3.1 per day poverty line (commonly used for middle-income countries)[10] were used to define poverty for the IHE indicator. Both were set at 2011 international prices and were converted to HK dollars in 2020 prices using the 2011 purchasing power parity exchange rates and consumer price indices. Individuals that were pushed below the poverty lines through OOP health expenditure were considered to experience IHE. For both indicators, proportion of patients experiencing CHE and IHE were determined, indicating the proportion at risk of financial hardship in this cohort.

Sensitivity analysis

In view of the study period coinciding with the Coronavirus disease 2019 (COVID-19) pandemic, participants were asked whether the patient's current utilization of healthcare and community services and resources were affected by the COVID-19 pandemic. In the sensitivity analysis, total annual cost of RD was estimated only among those who reported no difference in utilization.

Three sensitivity analyses were performed to assess the incidence of CHE and IHE. Since the estimated annual household income only accounted for patient's and caregiver's income, total household income might have been underestimated. To account for this, in the first sensitivity analysis, the HK median domestic household income of economically active households from the Census and Statistics Department was used instead. The second sensitivity analysis replaced all missing OOP expenditure values with median OOP spending among patients with the exact same RD who reported OOP health expenditure. If such data were not available, then the within-disease category median (within same version of CSRI-Ra) was used. The third sensitivity analysis was the combination of these two sensitivity analyses.

Statistical analysis

Demographics and cohort characteristics were summarized using descriptive statistics. Two-sample t-test was used to assess whether the annual mean cost estimates were significantly different between two groups. Age was regrouped to $\leq$18 and >18 years old; number of family members with RDs was regrouped to having one or more family members affected by RD versus those who do not have any other affected family members; years since diagnosis was regrouped to being diagnosed within or over five years.

The association between the independent variables and average annual cost was analyzed using generalized linear regression with gamma distribution and a log link function to obtain crude estimates of coefficients and 95% confidence interval (CI). Logistic regression was used to analyze independent variables against risk of CHE, and risk of IHE to obtain odds ratios. Multivariate regression simultaneously evaluated the association between outcomes of interest and different variables, including age, gender, years since being diagnosed, number of family members with RD(s), and whether the patient has received social security support or governmental allowance(s). Age, years since being diagnosed, and number of family members with RD(s) were analyzed as continuous variables. The significance level was set at $p < 0.05$ for two tails. All statistical analyses were conducted using STATA version 15.1.

Role of the funding source

Funders were not involved in the development of study design, data collection, data analysis, data interpretation or writing of report.

Results

A total of 325 CSRI-Ra responses were collected; 41 were excluded due to duplications, insufficient information provided or patient suffering from an undiagnosed disease. Among the 284 valid independent responses, 158 were self-completed by the RD patient and 126 were proxy-completed by the caregiver of the RD patient.

The characteristics of the RD patients were summarized in Table 1. Among adult patients, 20.4% required a proxy to complete the CSRI-Ra. A total of 106 unique RDs covering 13 RD categories were recorded. The majority of patients (97.5%) only had one RD diagnosis pertaining to one RD category.

Societal cost of RD

Total cost of RD was estimated at $484,256 (standard deviation (SD) $730,736; range $2920–$6,161,275) per patient per year (Table 2). Pediatric RD patients ($840,908; SD $954,250) had significantly higher annual costs compared to adult RD patients ($324,126; SD $534,329) ($p < 0.001$) (Table 3, Supplementary Fig. S1). The highest cost type was direct non-healthcare costs (40.0%), followed by direct healthcare costs (38.7%) and indirect cost (21.4%) (Table 2).

Direct healthcare costs

Direct healthcare cost was estimated to be $187,166 per patient per year (Table 3), mostly contributed by cost of medications (51.6%) and health services (45.4%). Patients who required drugs (61.3%) reported an average

Characteristics	Number of RD patients (%) (n = 284)
Gender	
Male	134 (47.2)
Female	150 (52.8)
Age	
≤18	88 (31.0)
19–64	185 (65.1)
≥65	11 (3.9)
Mean (SD)	31.5 (19.7)
RD category[b]	
Rare bone disease	17 (6.0)
Rare developmental defects during embryogenesis	67 (23.6)
Rare endocrine disease	4 (1.4)
Rare eye disease	4 (1.4)
Rare gastroenterologic disease	2 (0.7)
Rare hematologic disease	9 (3.2)
Rare immune disease	6 (2.1)
Rare inborn errors of metabolism	31 (10.9)
Rare neoplastic disease	3 (1.1)
Rare neurologic disease	107 (37.7)
Rare respiratory disease	8 (2.8)
Rare skin disease	4 (1.4)
Rare systemic or rheumatologic disease	24 (8.5)
Age at diagnosis[a]	
≤18	126 (44.4)
19–64	118 (41.5)
≥65	3 (1.1)
Mean (SD)	20.2 (19.4)
Years since being diagnosed[a]	
0–5	103 (36.3)
6–10	34 (12.0)
11–15	30 (10.6)
16–20	28 (9.9)
21–25	26 (9.2)
26–30	13 (4.6)
>30	13 (4.6)
Mean (SD)	11.8 (10.6)
Number of other family members with RD(s)[a]	
0	201 (70.8)
1	35 (12.3)
2	16 (5.6)
3	6 (2.1)
4	8 (2.8)
≥5	7 (2.5)
Education/employment status[a]	
Student	88 (31.0)
Full time employment	49 (17.3)
Part time employment	14 (4.9)
Housewife/househusband	16 (5.6)
Retired	25 (8.8)
Not in education/unemployed	70 (24.6)
Social security support/Governmental allowance(s) received by patient[c]	
Comprehensive social security assistance	43 (23.9)
Social security allowance: Normal disability allowance	80 (44.9)
Social security allowance: Higher disability allowance	60 (34.1)
Social security allowance: Normal/Higher old age living allowance	3 (1.1)
Community Care Fund Assistance Programs	11 (3.9)
Other scheme/allowance	6 (9.1)
Did not receive any social security support/ Governmental allowance	110 (37.0)
Member of patient support group(s)[a]	
No	57 (20.1)
Yes	223 (78.5)
Required care from paid or unpaid caregiver(s) in the past 6 months	
No	75 (26.4)
Yes	209 (73.6)
Any difference in utilization of healthcare and community services and resources as compared to the period prior to the COVID-19 pandemic?[a]	
No	157 (55.3)
Yes	103 (36.3)

COVID-19 Coronavirus disease 2019; RD rare disease; SD standard deviation. [a]There are missing data in this variable. [b]Seven patients are suffering from two different RDs. [c]27 patients received social security support/governmental allowance from more than one schemes, additional information in Supplementary Table S2.

Table 1: **Demographic characteristics of the 284 RD patients.**

Characteristics	Number of patients (%)	Direct healthcare cost	Direct non-healthcare cost	Indirect cost	Total cost
Gender					
Male	134 (47.2)	127,621	210,801	116,810	455,231
Female	150 (52.8)	240,360	178,148	91,676	510,184
Age[a]					
≤18	88 (31.0)	329,917	392,449	118,543	840,908
19–64	185 (65.1)	123,962	104,710	96,426	325,097
≥65	11 (3.9)	108,138	96,608	103,048	307,794
RD category[b]					
Rare bone disease	17 (6.0)	216,929	303,596	50,251	570,776
Rare developmental defects during embryogenesis	67 (23.6)	73,075	282,246	109,041	464,362
Rare endocrine disease	4 (1.4)	68,544	46,857	94,300	209,701
Rare eye disease	4 (1.4)	5213	154,110	221,919	381,242
Rare gastroenterologic disease	2 (0.7)	276,888	221,711	220,800	719,399
Rare hematologic disease	9 (3.2)	1,090,333	102,200	120,043	1,312,576
Rare immune disease	6 (2.1)	18,251	37,038	0	55,288
Rare inborn errors of metabolism	31 (10.9)	407,449	307,496	103,143	818,088
Rare neoplastic disease	3 (1.1)	41,967	291,610	58,904	392,481
Rare neurologic disease	107 (37.7)	173,922	155,423	120,769	450,115
Rare respiratory disease	8 (2.8)	144,185	40,334	132,972	317,491
Rare skin disease	4 (1.4)	30,618	3570	66,433	100,620
Rare systemic or rheumatologic disease	24 (8.5)	51,799	49,862	45,260	146,921
Number of other family members with RD(s)[a]					
0	201 (70.8)	230,907	210,838	104,782	546,401
1	35 (12.3)	52,236	188,323	110,474	351,033
2	16 (5.6)	30,665	42,458	129,775	202,899
3	6 (2.1)	94,156	114,156	79,377	287,689
4	8 (2.8)	42,972	226,089	59,038	328,099
≥5	7 (2.4)	25,271	57,743	3301	86,315
Years since being diagnosed[a]					
0–5	103 (36.3)	313,185	243,165	117,683	674,033
6–10	34 (12.0)	97,006	233,794	120,481	451,281
11–15	30 (10.6)	252,646	174,904	115,724	543,274
16–20	28 (9.9)	66,699	158,208	103,973	328,880
21–25	26 (9.2)	50,491	175,795	87,449	313,735
26–30	13 (4.6)	58,489	133,630	64,087	256,207
>30	13 (4.6)	56,933	125,887	92,554	275,373
Education/employment status[a]					
Student	88 (31.0)	206,242	375,534	100,653	682,429
Full time employment	49 (17.3)	131,464	42,052	39,629	213,145
Part time employment	14 (4.9)	398,611	53,596	59,224	511,431
Housewife/househusband	16 (5.6)	50,151	79,124	138,257	267,532
Retired	25 (8.8)	71,595	57,455	134,407	263,456
Not in education/unemployed	70 (24.6)	266,202	192,088	156,230	614,520
Social security support/Governmental allowance(s) received by patient[c]					
Received social security support/Governmental allowance	174 (61.3)	253,822	234,517	125,590	613,929
Did not receive any social security support/Governmental allowance	110 (38.7)	81,727	128,760	68,650	279,136
Total (range)	**284 (100.0)**	**187,166 (0–6,043,952)**	**193,555 (0–1,024,224)**	**103,535 (0–450,158)**	**484,256 (2920–6,161,275)**

RD rare disease. [a]There are missing data in this variable. [b]Seven patients are suffering from two different RDs. [c]27 patients received social security support/governmental allowance from more than one schemes.

Table 2: **Direct healthcare cost, direct non-healthcare cost, indirect cost, and total cost of RDs per patient per year ($–Hong Kong Dollars).**

of 5.4 different drugs. For the 84.2% of patients who reported utilization of hospital and/or community health services, an average of 9.5 visits per patient annually was recorded. For those who were admitted to the hospital (21.1%), each patient was admitted an average of 5.3 times annually.

Pediatric patients had significantly higher cost of health services (p = 0.004), medical resources and consumables (p = 0.004) and total direct healthcare costs (p = 0.013) than adult patients (Table 3).

Direct non-healthcare costs

Direct non-healthcare was the highest among the three cost types, at $193,555 per RD patient per year (Table 3). It was significantly higher in pediatric ($392,449) than adult RD patients ($104,225) (p < 0.001), mainly because of the cost of informal care support and special education.

Informal care support provided by the patient's parents (67.8%) and spouse (23.0%) accounted for 66.2% of the total direct non-healthcare costs, with 87.5% and 54.1% of pediatric and adult RD patients requiring informal care support respectively.

Among the 88 RD patients who were receiving education, 51.1% were enrolled in special schools. Annual average cost of special education and extra visits to school professionals in mainstream schools was estimated at $87,292 per pediatric patient.

Indirect costs

Indirect cost was estimated at $103,535 per patient per year, with 67.7% contributed by caregiver's productivity losses (Table 3).

Among patients who received informal care support (n = 183), 68.9% of their unpaid caregiver's employment was affected (81.8% of pediatric patients, 59.4% of adult patients) (Supplementary Table S3). Cost of forced retirement/unemployment and absenteeism in unpaid caregivers was estimated to be $43,538 and $26,517 per patient per year, respectively (Table 3).

Employment was affected in 67.6% of the 102 adult patients who were employed full- or part-time prior to being diagnosed with a RD (Supplementary Table S3). Total productivity loss was estimated at $46,550 per adult patient per year.

Territory-wide socio-economic cost of RD in HK

The total annual cost per patient was combined with the prevalence of RDs in HK (1.5% of the HK population).[8] Using the official government 2020 year-end population estimates and the RD pediatric and adult

	Average annual cost per patient			
	All patients (n = 284)	≤18 years old (n = 88)	>18 years old (n = 196)	P-value
Direct healthcare costs				
Health services	84,883	157,127	52,446	0.004
Medications	96,505	163,791	66,296	0.170
Medical resources and consumables	1386	2132	1051	0.004
Community medical services	4392	6867	3281	0.357
Total direct healthcare costs	**187,166**	**329,917**	**123,074**	**0.013**
Direct non-healthcare costs				
Professional care	14,879	18,949	13,052	0.906
Informal care	128,158	259,823	69,043	<0.001
Special education and employment services	31,876	87,292	6995	<0.001
Residential or foster care placements	8052	13,860	5445	0.055
Home modification	550	480	581	0.529
Transportation	10,040	12,044	9139	0.259
Total direct non-healthcare costs	**193,555**	**392,449**	**104,255**	**<0.001**
Indirect costs				
Productivity loss by RD patient:	*32,126*	*0*	*46,550*	*<0.001*
Loss due to forced retirement/unemployment	27,211	0	39,429	<0.001
Absenteeism (reduced working hours and days)	4915	0	7122	0.011
Productivity loss by caregiver:	*70,055*	*115,135*	*49,815*	*<0.001*
Loss due to forced retirement/unemployment	43,538	70,255	31,543	0.001
Absenteeism (reduced working hours and days)	26,517	44,880	18,272	0.003
Health services utilized by patient's family member(s)	1354	3408	433	0.012
Total indirect costs	**103,535**	**118,543**	**96,797**	**0.168**
Grand total ($, SD)	**484,256 (730,736)**	**840,908 (954,250)**	**324,126 (534,329)**	**<0.001**

RD rare disease.

Table 3: **Breakdown of direct healthcare cost, direct non-healthcare cost, indirect cost, and total cost of RDs in pediatric and adult patients.**

	CHE			IHE	
	10% threshold	25% threshold	40% threshold	$1.9 poverty line	$3.1 poverty line
Baseline estimates	36.3%	23.9%	17.3%	8.5%	8.8%
Sensitivity analysis 1: Household income estimated using Hong Kong median domestic household income of economically active households	21.8%	11.6%	7.7%	3.2%	3.2%
Sensitivity analysis 2: Missing OOP expenditure values replaced by median; household income estimated using CSRI-Ra data	40.5%	26.4%	18.3%	9.5%	9.9%
Sensitivity analysis 3: Missing OOP expenditure values replaced by median; household income estimated using Hong Kong median domestic household income of economically active households	23.6%	12.7%	8.5%	3.9%	3.9%

CSRI-Ra Client Service Receipt Inventory for the RAre disease population; **CHE** Catastrophic health expenditure; **IHE** Impoverishing health expenditure; **OOP** out-of-pocket.

Table 4: **Estimates of catastrophic and impoverishing OOP health expenditure.**

patient ratio, the number of RD patients in HK was estimated to be 111,573 (38,443 pediatric patients and 73,130 adult patients).[8,20] The aggregate territory-wide annual cost of RD was estimated to be $56.03 billion in 2020 (Supplementary Table S4).

Out-of-pocket health expenditure and financial hardship

Annual total OOP health expenditure was estimated at $51,840 (SD $130,414, range $0–$975,400) per patient per year (Supplementary information 5, Supplementary Table S5). Among those with OOP health expenditure in the reported period (n = 217), 15.7% had to pay >$100,000 OOP for healthcare annually, with an average of $327,245 per patient per year among these patients, (Supplementary Table S6).

The incidence of CHE for this cohort at the 10%, 25% and 40% thresholds was found to be 36.3%, 23.9% and 17.3%, respectively (Table 4). The incidence of CHE at the 10% threshold was found to be the highest in patients with rare gastroenterologic disease (100%), followed by patients with rare neoplastic disease (66.7%) and rare hematologic disease (55.6%); 66.7% of these patients were also experiencing CHE at both the 25% and 40% thresholds.

The incidence of IHE was 8.5% at the $1.9 per day poverty line and 8.8% at the $3.1 per day poverty line (Table 4). The incidence of IHE at the $1.9 per day poverty line was found to be highest in patients with rare neoplastic disease (66.7%), followed by patients with rare endocrine disease and rare respiratory disease (both 25.0%) and rare hematologic disease (22.2%).

Association between independent variables and cost of RDs

Multivariate regression analyses revealed that older age ($p < 0.001$), longer years since diagnosis ($p = 0.026$) and having more family members with RDs(s) ($p = 0.023$) were negatively associated with the annual mean total cost of RDs (Supplementary Table S7). Patients receiving social security support or governmental allowance(s) had significantly higher total mean RD costs ($p < 0.001$).

Association between independent variables and incidence of CHE and IHE

Regardless of threshold, individuals with longer years since diagnosis were less likely to experience CHE, statistically significant at $p \leq 0.021$, while older patients ($p \leq 0.012$) and patients receiving social security support/governmental allowance ($p \leq 0.004$) were more likely to experience CHE (Supplementary Table S8). No variables reached statistical significance in the multivariate model for IHE (Supplementary Table S9).

Sensitivity analyses

A total of 157 (55.3%) patients reported no difference in service and resource utilization between the study period and prior to the COVID-19 pandemic. In this group of patients, annual average total cost of RD was estimated at $441,951 (SD $700,645; range $2920–$6,161,275) per patient. Indirect and direct non-healthcare costs were 6.9% and 10.2% lower than their respective baseline estimates (Supplementary Table S10). Using these estimates, the territory-wide socio-economic cost of RDs in HK was projected to be $53.35 billion in 2020, suggesting that the COVID-19 pandemic caused $2–3 billion difference in RD costs.

Three sensitivity analyses were performed to assess the baseline estimates of CHE and IHE incidence. CHE varied from 21.8% to 40.5% at the 10% threshold, 11.6%–26.4% at the 25% threshold and 7.7%–18.3% at the 40% threshold (Table 4). IHE varied from 3.2% to 9.5% at the $1.9 per day poverty line and 3.2%–9.9% at the $3.1 per day poverty line (Table 4).

Multivariate generalized linear regression from sensitivity analysis revealed that older age was significantly associated with lower costs, and that patients receiving social security support or governmental allowance(s) had significantly higher total mean costs (Supplementary Table S11).

Discussion

This study is the first to systematically evaluate the socio-economic burden of RDs and the impact of RD-related OOP health expenditure on financial hardship.

From a cohort with 106 unique RDs across 13 categories in HK, the average cost of RD was estimated to be a minimum of HK$441,951 (US$56,660) per patient per year, with 38.9% in direct healthcare costs and 61.1% in direct non-healthcare and indirect costs. With one in 67 people living with RDs in HK, the territory-wide economic impact of RDs, was estimated to be over HK$53 billion (US$6.8 billion) in 2020. Notably, although RD patients only account for 1.5% of the HK population, the estimated territory-wide direct healthcare costs of RDs was 11.4% of the total healthcare expenditure in HK.[8,21] Findings from this study highlight areas that should be prioritized to help the RD population receive accessible, affordable and effective healthcare without experiencing financial hardship (Fig. 1).

From a global perspective, it is evident that high costs of RDs are not unique to HK (Table 5).[13,14] Although estimates are only available for some European countries and the United States, the societal cost estimate from this study was comparable to other jurisdictions. The total cost of RDs per patient per year is consistently upwards of HK$170,000 (US$21,794) across all existing literature (Supplementary information 6).[13,14] Furthermore, the EverydayLife foundation found that the societal costs of RDs were higher than the cost of common diseases in the United States.[14] Although only a few studies have evaluated the cost of common diseases within HK,[22–26] the cost of RDs from a societal perspective was still the highest across all diseases (Supplementary Table S12). With RDs being at least HK$300,000 (US$38,461) more costly per patient compared to other common diseases, an accurate breakdown of direct and indirect costs of RDs is crucial in guiding decision making for the RD population.

Direct healthcare costs

Previous studies on direct healthcare costs of RDs reported disproportionately longer hospital stays, more readmissions and higher inpatient and outpatient costs, indicating unusually high utilization of healthcare services by RD patients.[6–8] However in this cohort, cost of medications was more significant. This is likely driven by orphan drugs that target RDs or diseases without existing methods of treatment since less than 3% of RDs have suitable drug treatment, with available drugs costing 13.8 times more than conventional drugs.[27,28] Specific RD legislations and policies need to be in place to ensure accessibility and affordability of healthcare services and orphan drugs to reduce direct healthcare costs.

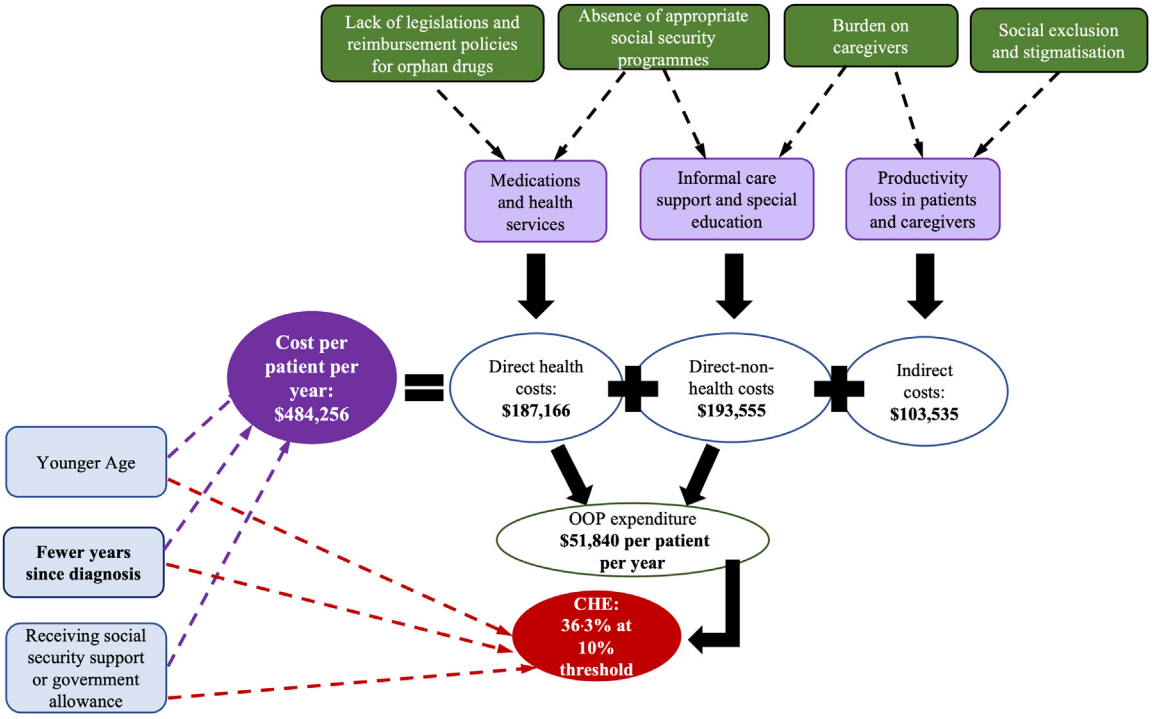

Fig. 1: Breakdown and determinants of cost for the rare disease population in Hong Kong. All presented values are baseline estimates in Hong Kong dollars. Variables in circles are different measures of cost. Purple boxes indicate the highest contributor of a specific cost type. Green boxes are potential drivers of the highest contributor of each cost type. Blue boxes are factors that drive up the different measures of cost, fewer years since diagnosis (bolded) was as associated with both total cost and CHE. **CHE** catastrophic health expenditure; **OOP** out-of-pocket; **RD** rare disease.

Jurisdiction	Number of RDs included in the study	Total cost of RD per patient per year	
		Local currency	Hong Kong Dollars ($, adjusted to 2020 prices)
Bulgaria[a]	8	€ 14,833	178,759
France[a]	10	€ 27,521	331,676
Germany[a]	9	€ 60,213	725,661
Hungary[a]	8	€ 14,342	172,839
Italy[a]	10	€ 39,494	475,963
Spain[a]	9	€ 37,187	448,165
Sweden[a]	10	€ 39,164	471,988
United Kingdom[a]	9	€ 36,485	439,709
United States[15]	379	$62,141	487,778
Hong Kong (this study)	106	–	441,951[b]

RD rare disease. [a]Estimated from the BURQOL-RD series (Supplementary information 6). [b]Based on cost estimates from sensitivity analysis.

Table 5: **Total costs of RDs from a societal perspective in different jurisdictions.**

Financial hardship resulting from high OOP health expenditure

Risk of financial hardship was prevalent in this cohort. The lowest incidence rate obtained through sensitivity analysis in this study (21.8%) was substantially higher than the global estimate of CHE in 2015 (12.7% at SDG 10% threshold).[29] Similarly, a much higher IHE incidence rate (baseline $1.90 threshold: 8.5%, $3.10 threshold: 8.8%) was observed in our study compared to an estimated IHE incidence rate in 2010 across 122 countries ($1.90 threshold: 1.23% and $3.10 threshold: 1.35%).[10] These findings are alarming considering the progressive health financing structures in HK and suggestive of the inherent risk of poverty and vulnerability for RD patients. Currently, approval of existing cost-sharing or reimbursement policies in HK (i.e. "Samaritan Fund"[30]) do not cover novel RD drugs, and eligibility is dependent on meeting stringent criteria. Therefore, prepayment systems and reimbursement policies tailored to the RD population are invaluable in reducing financial hardship.[19,29]

Importance of RD diagnosis

Longer years since diagnosis was consistently associated with lower total cost and CHE incidence rates. Similarly, a recent study in Germany estimated that a timely diagnosis of RDs would have reduced total costs by 32–41%, highlighting the importance of experts and appropriate diagnostic tests.[31] Clear disease etiology revealed through an appropriate diagnosis allows for more effective symptom-driven treatments and improved coordination of care whilst avoiding unnecessary and costly diagnostic testing and interventions.[32,33] From a societal perspective, it allows a patient's condition to be visible,[33] enabling access to healthcare and social programs that reduce economic impacts to the healthcare system and to patients and their families.[32] The International Rare Disease Research Consortium has acknowledged these benefits, setting the goal for all RD patients to receive an accurate diagnosis within one year of medical attention.[34]

However, limited medical knowledge, poor coordination of care and limited access to genetic testing results in diagnostic odysseys of up to seven years.[2,35] The Hong Kong Genome Project was recently launched to target this in the local population. Through whole-genome sequencing of unique undiagnosed patients, new information could aid precise diagnoses and diagnosis-predicated precision medicine that would potentially improve patient outcomes in the future.[36]

Impact of receiving social security support/ governmental allowance

Patients receiving government allowance had higher total costs, OOP health expenditure and higher risk of CHE based on the regression models. Social security programs are in place to tackle the problem of accessibility that is associated with high costs of RD treatments. However, successful applications for such funding are conditional on the patient meeting stringent requirements. As such, patients who receive governmental allowance are potentially more likely to have conditions that require higher utilization of healthcare resources to manage disease symptoms. This also suggests that the current governmental allowance and support schemes may not be sufficient to cover the high healthcare costs incurred by patients with debilitating RDs. Therefore, the RD population might benefit from policies that are specifically tailored and unique to the challenges RD patients face.[37] This ultimately requires collaboration between the government, healthcare providers and the community to reduce financial burden and hardship within the RD population.

Hidden costs: direct non-healthcare costs and indirect costs

Direct non-healthcare and indirect costs account for over 60% of the total societal cost of RDs in this cohort.

Similarly, the EverdayLife foundation study also reported indirect and non-medical costs accounting for 57% of overall economic impact.[14]

As discrimination and lack of awareness remains rooted within society, continuous systemic exclusion of the RD population further contributes to significant productivity losses.[38] While previous surveys have qualitatively described financial struggles resulting from workplace stigma,[38] we quantitatively report that employment was impacted in 67.6% of the RD patients in this cohort, resulting in productivity loss of $46,550 (US$5968) per adult patient per year.

Indirect costs also arise from impacts on caregivers. Approximately 75% of RD patients are children who require permanent care.[39] This harbors a unique set of challenges in RD caregivers. In this cohort, informal care contributes significantly to total direct non-healthcare costs at $128,158 (US$16,430) per patient annually. Moreover, we report significant spill-over effects on the caregiver's overall productivity ($70,055 (US$8981) per patient per year), which causes financial strain and hardship for the caregivers themselves. Therefore, caregivers must be considered when planning for the RD population.

A collaborative approach for RDs

The RD population faces unique challenges.[33] Therefore, the management of RDs should be treated differently to common diseases. Future planning and allocation of resources for the RD population in HK should consider all the various dimensions of the impact of RDs through a patient-centered and multidisciplinary approach.

Bridging the gap between policy and practice requires increased engagement and education within the community. While civil society groups play an advocating role, governments must place emphasis on improving public education on RDs and implementing appropriate legislations and policies.[40,41] On a global scale, the recent adoption of the UN resolution for RDs has highlighted the impact of the collaboration between member states in improving the 'integration of RDs in the agenda and priorities of the UN system'. Through this global campaign, the needs of the RD community can be highlighted and met through healthcare and social care planning, reducing its societal impacts and bringing RD as a collective group one step closer to achieving UHC.[42]

Strengths and limitations

This is the first study within the Asia Pacific region to comprehensively evaluate the socio-economic impact experienced by a heterogeneous sample of RDs. To the best of our knowledge, this is the first and only study to estimate both RD societal costs and related financial hardship within the same cohort. Findings from two indicators highlighted the increased risk of financial hardship among the RD population. Nevertheless, CHE and IHE are multi-dimensional measures that should be interpreted cautiously. They are dependent on a combination of OOP health expenditures, household income and effective prepayment mechanisms. In this study, CHE and IHE were evaluated along with societal costs. This effectively assesses financial hardship and monitors UHC, potentially influencing future planning and allocation of resources to support the RD population.

Our study has limitations. Firstly, the study period coincided with the COVID-19 pandemic in HK, potentially impacting healthcare utilization and costs. This was considered in sensitivity analyses by estimating costs using data from participants who reported no difference in service and resource utilization during the COVID-19 period. Secondly, the household income data used to estimate CHE and IHE included patient and caregiver income, but did not include income from additional family members, potentially resulting in underestimation of total household income. This was also considered in three sensitivity analyses. Thirdly, recruitment was done on a voluntary, self-selection basis. As such, the study population may not be representative of all RD patients and their families, with a potential to be skewed towards higher expenditure as patients and families incurring higher OOP expenditure might be more motivated to participate. Finally, limited data in certain RD categories precluded subgroup analysis for the comparison of costs between RD groups. In particular, undiagnosed patients encompass a large proportion of the RD population. Although beyond the scope of this study, it is acknowledged that undiagnosed patients face unique challenges and should be formally investigated in future studies.

Conclusion

This study is the first to illustrate the multi-faceted nature of the socio-economic impact of RDs through estimation of both societal costs and risk of financial hardship. Inclusion of RD population in Universal Healthcare Coverage planning requires close coordination between governments, healthcare systems and the community to provide holistic care and system reforms. This study highlights the needs of an often-forgotten population, offering findings to guide resource allocation and policy implementation to alleviate the high economic impact on the RD population as a whole.

Contributors

CCYC, MK and BHYC contributed to the conception and design of the study. CCYC, YNCN, ACYL carried out data collection and data cleaning. CCYC, NYTN and WHSW performed the statistical analyses and were involved in data organization and presentation. CCYC and NYTN drafted the manuscript. YNCN, ACYL, JLFF, MCYC, WHSW, SLL, MK and BHYC critically reviewed the manuscript with suggestions for improvement and revision. CCYC, SLL and BHYC obtained funding. MK and BHYC oversaw and supervised the project. All authors contributed to the overall data interpretation, reviewed, and approved the final draft for submission.

Data sharing statement

Upon reasonable request, the study protocol, informed consent forms, and individual participant data reported in this article, after de-identification, will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Data will be available from the corresponding authors up to five years following publication.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100711.

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