Socio-economic burden and health-related quality of life in patients with rare diseases during the COVID-19 pandemic: abridged secondary publication

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KEY MESSAGES

1. In Hong Kong, total costs for rare disease were estimated to be HK$518 420 per patient per year; >60% of costs were attributable to direct non-healthcare and indirect costs.
2. In Hong Kong, health-related quality of life, in terms of utility score, was significantly lower in patients with rare disease than in patients with other chronic diseases (0.52 vs 0.87-0.88).
3. Higher socio-economic costs for rare diseases were associated with lower utility scores, younger age, shorter duration since diagnosis, and receipt of governmental allowance.
4. During the COVID-19 pandemic, patients and caregivers who reported changes in service or resource utilisation had significantly lower utility scores than those who reported no changes.

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Introduction

Among European populations, rare diseases (RDs) are defined as conditions that affect <50 in 100 000 individuals.[1] Patients with RDs experience complex healthcare challenges and lifelong disabilities, both of which have detrimental impacts on health-related quality of life (HRQoL), which comprises physical, mental, and social well-being, as well as healthcare costs. This study aimed to estimate the socio-economic cost of RDs from a societal perspective, evaluate the HRQoL of patients with RDs and their caregivers, identify factors associated with RD cost and HRQoL, and evaluate the impact of COVID-19 on the socio-economic burden and HRQoL of RDs.

Methods

This prospective cross-sectional study was carried out between March and October 2020 during the COVID-19 pandemic. Patients with RDs or their caregivers were recruited. The validated Client Service Receipt Inventory for the RD population was used to collect demographic and resource utilisation data.[2] A prevalence-based bottom-up approach was implemented to quantify service and resource utilisation from a societal perspective. Direct healthcare costs (health services, medications, medical resources/consumables, community medical services) and direct non-healthcare costs (professional care, informal care, special education and employment, residential/foster care placements, home modification, transportation) were based on utilisation records, which were valued according to 2022/23 unit costs. Indirect costs were mainly based on labour productivity losses resulting from RD, estimated using the human-capital approach. Territory-wide socio-economic burden was derived by combining the average total annual cost and prevalence of RDs in Hong Kong, based on 2023 year-end population estimates.[3]

The EuroQol 5-Dimension 3-Level (EQ-5D-3L) was used to assess HRQoL in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[4] In cases that patients required a proxy respondent, caregiver HRQoL data were also collected. Utility scores for each patient and caregiver were generated based on the Hong Kong value set and the reverse crosswalk algorithm to facilitate comparison with other studies. The EuroQol visual analogue scale (EQ-VAS) for overall health perception was also used.

Participants were asked whether there was any difference in healthcare and community services/resource utilisation compared with the period prior to the COVID-19 pandemic. Total costs and HRQoL were compared between participants who reported differences in utilisation and those who did not.

Linear regression of independent variables against average annual cost and HRQoL was conducted. Multivariate regression analyses were performed to simultaneously evaluate the association of mean annual costs and HRQoL with different variables. The significance threshold was set at $P<0.05$ (two-tailed).

Results

In total, responses from 325 participants were collected; 41 were excluded due to duplication, insufficient data, or invalid responses. The remaining 284 responses, covering 106 unique RDs, were included in the analysis; 158 responses were patient-completed and 126 were proxy-completed by caregivers.

The mean total cost of RDs was estimated at HK$518 420 per patient per year. The highest cost category was direct non-healthcare costs (39.7%), followed by direct healthcare costs (38.8%) and indirect costs (21.5%) [Table 1]. Direct healthcare costs were estimated at HK$201 114 per patient per year; most were attributed to health services (48.9%) and medications (48.0%). Direct non-healthcare costs were estimated at HK$206 065 per patient per year. Informal care represented 66.7% of total direct non-healthcare costs; 64.4% of patients received care from unpaid caregivers. Among the 88 patients who were receiving education during the study period, 51.1% required schooling in special schools. Indirect costs were estimated at HK$111 240 per patient per year. Patient and caregiver productivity losses represented 31.1% and 67.6% of total indirect costs, respectively. Based on the estimated prevalence of RDs in Hong Kong, the aggregate territory-wide annual cost of RDs was estimated to exceed HK$60.21 billion in 2023.

Regarding patient HRQoL, the mean utility score was 0.52; 30 (10.6%) patients reported negative utility scores. Patients with rare neurological diseases had the lowest mean utility score relative to other patients (0.33 vs 0.64, P<0.001). The mean EQ-VAS score was 66.3. HRQoL data from six other studies across various jurisdictions were pooled with the mean utility score obtained in this study. In total, 12 622 patients with RDs were included; the mean pooled utility score was 0.59 (95% confidence interval=0.52-0.66, I^2=98.65%, Q=187.60, degree of freedom=6, P<0.0001).

Regarding caregiver HRQoL, the mean utility score among 96 caregivers (0.80) was correlated with the patient utility score (r=0.27, P=0.009). The mean EQ-VAS score among 107 caregivers was 73.1.

During the COVID-19 pandemic, 103 (36.3%) patients reported changes in service and resource utilisation compared with the prior period. The mean total cost did not significantly differ between patients who reported changes in utilisation and those who did not (HK$562 802 vs HK$469 246, P=0.294). The mean utility score was lower among patients who reported changes in resource utilisation than among those who reported no such changes (0.38 vs 0.62, P<0.001). Caregivers of patients who reported changes in healthcare and resource utilisation also reported lower utility scores (0.74 vs 0.85, P<0.001).

Lower total RD cost was associated with older age, longer duration since diagnosis, residence in public housing or subdivided flats, and higher patient utility scores (Table 2). The receipt of social security support or governmental allowance was associated with higher total RD costs and lower patient utility scores. Residence in public housing or subdivided flats was associated with a lower utility score among caregivers.

Discussion

In Hong Kong, the societal cost of RDs per patient is >HK$200 000 higher than that of other common diseases, including type 2 diabetes, rheumatoid arthritis, epilepsy, and cerebellar ataxia. The cost of RDs in Hong Kong is comparable to that in other regions in Europe[5] (Table 3). High utilisation of healthcare services is likely driven by the costs of symptomatic therapy and orphan drugs used to treat RDs. Currently, there are insufficient policies to support access to orphan drugs in Hong Kong. A diagnosis of RD is important to reduce unnecessary medical procedures and increase the visibility of patients' conditions within society, thus enabling access to healthcare and social programmes that can potentially reduce the societal cost of RDs. This relationship was supported by our findings, in which the number of years since diagnosis was associated with total cost. In addition to medical challenges, social exclusion contributes to costs by preventing integration of the RD population into the education and employment sectors, which manifests as productivity loss. Although the Disability Discrimination Ordinance was implemented to prevent job inequalities, specific policies are required to address the unique needs of the RD population.

The utility scores of patients (0.52) and caregivers (0.80) were both significantly lower than that of the general population (0.92); they were also lower than scores reported for other chronic diseases, including cancer (0.87) and heart disease (0.88). Patients with neurological RDs had the lowest HRQoL. This may be due to the limited availability of symptomatic therapies for neurological diseases, resulting in persistent mobility problems that cause high levels of pain and discomfort. Patients with 'rare developmental defects during embryogenesis' experienced relatively better HRQoL than other RD categories. These patients were born with disabilities and may not have experienced a change in identity as encountered by patients with acquired conditions. These findings underscore the importance of interventions to promote coping strategies that foster a sense of control over the consequences of disease. Caregiver HRQoL was also lower than that of the general population. This appears to be driven by a high psychological burden, as indicated by more problems related to the anxiety and depression dimension of the EQ-5D-3L, and by intensive

TABLE 1. Direct healthcare cost, direct non-healthcare cost, indirect cost, total cost, and mean utility score of rare diseases (RDs) per patient per year (n=284).

Characteristic	No. (%) of patients	Direct healthcare cost, HK$	Direct non-healthcare cost, HK$	Indirect cost, HK$	Total cost, HK$	Mean ± standard deviation utility score
Sex						
Male	134 (47.2)	140 515	224 051	125 325	489 891	0.51±0.37
Female	150 (52.8)	255 250	189 998	98 658	543 906	0.54±0.34
Age, y						
≤18	88 (31.0)	355 059	417 501	126 914	899 474	0.46±0.41
19-64	185 (65.1)	132 896	111 640	103 806	348 342	0.57±0.32
≥65	11 (3.9)	116 857	102 639	110 888	330 384	0.32±0.30
RD category (seven patients had two different RDs)						
Rare bone disease	17 (6.0)	257 905	324 862	54 144	636 910	0.65±0.25
Rare developmental defects during embryogenesis	67 (23.6)	77 464	301 165	117 388	496 017	0.63±0.30
Rare endocrine disease	4 (1.4)	78 829	49 138	101 475	229 442	0.67±0.24
Rare eye disease	4 (1.4)	5 773	161 928	223 568	391 269	0.73±0.17
Rare gastroenterological disease	2 (0.7)	339 195	237 680	237 600	814 475	0.41±0.19
Rare haematological disease	9 (3.2)	1 101 056	107 224	129 188	1 337 468	0.81±0.18
Rare immune disease	6 (2.1)	19 694	38 559	0	58 253	0.76±0.32
Rare inborn errors of metabolism	31 (10.9)	448 828	327 657	110 995	887 479	0.45±0.50
Rare neoplastic disease	3 (1.1)	47 705	307 064	63 478	418 248	0.82±0.15
Rare neurological disease	107 (37.7)	184 575	165 124	130 026	479 726	0.33±0.31
Rare respiratory disease	8 (2.8)	150 536	42 903	143 028	336 467	0.55±0.17
Rare skin disease	4 (1.4)	35 306	3 577	71 487	110 370	0.67±0.13
Rare systemic or rheumatological disease	24 (8.5)	60 000	52 788	48 704	161 492	0.80±0.17
No. of other family members with RDs (some data missing)						
0	201 (70.8)	246 231	224 389	112 500	583 120	0.48±0.37
1	35 (12.3)	52 133	201 531	118 898	372 561	0.65±0.29
2	16 (5.6)	34 667	44 821	139 668	219 156	0.56±0.23
3	6 (2.1)	110 976	118 533	85 416	314 925	0.51±0.27
4	8 (2.8)	50 251	240 830	63 530	354 611	0.53±0.53
≥5	7 (2.5)	27 674	60 196	3 552	91 422	0.79±0.30
Years since diagnosis (some data missing)						
0-5	103 (36.3)	334 873	259 139	126 654	720 666	0.48±0.38
6-10	34 (12.0)	106 031	248 683	129 648	484 361	0.50±0.39
11-15	30 (10.6)	261 520	184 315	124 596	570 431	0.62±0.29
16-20	28 (9.9)	78 375	167 165	111 889	357 429	0.57±0.35
21-25	26 (9.2)	52 213	188 074	94 103	334 390	0.53±0.36
26-30	13 (4.6)	62 061	143 849	68 964	274 874	0.46±0.36
>30	13 (4.6)	59 101	135 459	99 603	294 164	0.42±0.39
Education/employment status (some data missing)						
Student	88 (31.0)	227 807	399 106	107 617	734 530	0.53±0.39
Full-time employment	49 (17.3)	134 348	44 278	42 635	221 261	0.73±0.24
Part-time employment	14 (4.9)	401 474	56 130	63 733	521 337	0.53±0.24
Housewife/househusband	16 (5.6)	55 709	84 264	148 785	288 758	0.45±0.22
Retired	25 (8.8)	83 267	60 611	144 654	288 531	0.45±0.29
Not receiving education/unemployed	70 (24.6)	284 494	205 688	168 285	658 466	0.39±0.38
Type of housing (some data missing)						
Public housing/subdivided flats	122 (43.0)	76 279	184 038	113 854	374 172	0.45±0.33
Rented flat	36 (12.7)	379 437	219 749	111 058	710 244	0.57±0.41
Owned flat	114 (40.1)	291 621	225 472	108 036	625 128	0.60±0.35
Other	11 (3.9)	82 347	195 890	126 167	404 405	0.46±0.39
Social security support/governmental allowance						
Yes	174 (61.3)	269 181	249 789	134 873	653 803	0.45±0.35
No	110 (38.7)	93 445	136 966	73 857	304 268	0.64±0.34
Service/resource utilisation during COVID-19 pandemic (some data missing)						
Affected	103 (36.3)	184 132	240 150	138 521	562 802	0.38±0.38
No difference	157 (55.3)	180 602	185 293	103 351	469 246	0.62±0.30
Total	**284 (100.0)**	**201 114**	**206 065**	**111 240**	**518 420**	**0.52±0.36**

TABLE 2. Independent factors associated with total cost, patient utility score, and caregiver utility score.

Factor	Total cost, HK$		Patient utility score		Caregiver utility score	
	Adjusted coefficient (95% confidence interval)	Adjusted P value	Adjusted coefficient	Adjusted P value	Adjusted coefficient	Adjusted P value
Older age	-8254 (-13 156 to -3 352)	0.001	<0.001	0.891	-0.002	0.050
Female sex	113 058 (-69 799 to 295 915)	0.224	0.030	0.519	0.030	0.275
Longer duration since diagnosis	-9308 (-18 546 to -69)	0.048	0.002	0.473	0.002	0.200
Higher number of family members with rare diseases	-35 392 (-103 012 to 32 227)	0.303	0.017	0.308	0.008	0.574
Residence in public housing/subdivided flats	-289 481 (-476 905 to -102 058)	0.003	-0.089	0.059	-0.109	<0.001
Receipt of social security support/ governmental allowance	241 605 (41 627 to 441 582)	0.018	-0.196	<0.001	-0.055	0.095
Higher patient utility score	-485 183 (-747 209 to -223 157)	<0.001	-	-	-	-

caregiving responsibilities leading to productivity losses. Programmes and policies for patients with RDs should consider empowering and supporting caregivers.

The COVID-19 pandemic did not significantly affect the total cost of RDs, potentially due to the essential medical needs of affected patients. In contrast, the utility scores of patients with RDs and their caregivers were significantly lower among those who reported differences in healthcare and resource use during the pandemic. Limited access to healthcare services during this period might have generated uncertainty regarding disease management, negatively affecting psychological well-being. The detrimental impact of the pandemic on costs and HRQoL highlights the importance of maintaining effective RD management during public health crises.

This study highlights the unique needs of patients with RDs, particularly during health emergencies. Interventions for the RD population should address multiple dimensions of disease impact through a patient-centred and multidisciplinary approach. Civil society groups and governments play important roles in facilitating the implementation of appropriate legislation and policies.

This study has several limitations. First, recruitment was voluntary, and the study population may not be representative of the RD population in Hong Kong. Second, detailed subgroup analyses comparing costs and HRQoL across RD categories were not feasible due to limited data in certain groups. Third, the EQ-5D-3L measure of HRQoL may not be generalisable to paediatric patients; however, the proxy version has been validated. Finally, caregiver HRQoL results may only be representative of patients who were unable to complete the questionnaire independently.

TABLE 3. Total costs of rare diseases (RDs) from a societal perspective in different regions.

Region[5]	No. of RDs included	Year of publication, year of cost estimation	Total cost of RDs per patient per year, HK$ adjusted to 2022/23 prices
Bulgaria	8	2016, 2012	183 254
France	10	2016, 2012	340 007
Germany	9	2016, 2012	743 899
Hungary	8	2016, 2012	177 188
Italy	10	2016, 2012	487 927
Spain	9	2016, 2012	459 425
Sweden	10	2016, 2012	483 850
United Kingdom	9	2016, 2012	450 752
United States	379	2022, 2019	499 923
Germany, France, and Italy	23	2023, 2021	1 001 542
Turkey	>7	2023, 2020	26 124
Germany	3	2023, 2019	1 678 255
Hong Kong	106	2023	518 420

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1. Ng YNC, Ng NYT, Fung JLF, et al. Evaluating the health-related quality of life of the rare disease population in Hong Kong using EQ-5D 3-Level. Value Health 2022;25:1624-33.
2. Chung CCY, Ng NYT, Ng YNC, et al. Socio-economic costs of rare diseases and the risk of financial hardship: a cross-sectional study. Lancet Reg Health West Pac 2023;34:100711.

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