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Impact of Choice of Tariff When Calculating Clinically Meaningful EQ-5D Scores in Metabolic Dysfunction-Associated Steatohepatitis

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Keywords: country-specific tariff | EQ-5D-5L health utilities | metabolic dysfunction-associated steatohepatitis | real-world

ABSTRACT

Background & Aims: Self-reported health varies across countries, as populations attribute different degrees of value to EQ-5D domains. Country-specific EQ-5D tariffs were developed to account for this but are not always stated in the literature. We aim to assess the reporting of EQ-5D in the literature and the impact of applying country-specific tariffs.

Methods: We reviewed literature-reported EQ-5D utilities for patients with metabolic dysfunction-associated steatohepatitis versus real-world EQ-5D utilities from the Adelphi Real World Non-alcoholic steatohepatitis Disease Specific Programme (DSP), a cross-sectional survey in France, Germany, Italy, Spain, the United Kingdom and the United States. Matching-adjusted indirect comparison analysis balanced DSP data with literature studies by age, sex, comorbidities and fibrosis stage. DSP utility scores generated using national tariffs were compared with literature utilities using weighted t tests.

Results: Ten studies with varying recruitment criteria, patient demographics and clinical characteristics were identified. Country-specific tariffs were not used or not reported. EQ-5D utilities varied, reflecting geographic, clinical and demographic characteristics. The comparison of literature and matched utilities derived using DSP data and five national tariffs revealed ≥ two comparisons for each study with a difference not exceeding the minimal clinically important difference versus the matched DSP value.

Conclusions: Literature-reported EQ-5D utilities vary considerably depending on study methodology and country-specific EQ-5D tariff, and even if stated may not always use the most appropriate tariff. This suggests a need for consistent use of country-specific tariffs and sensitivity analyses confirming results and conclusions that include EQ-5D-based utility measurement to inform decision-making by health authorities.

Abbreviations: DSP, Disease-Specific Programme; GAIN, Global Assessment of the Impact of NASH; HRQoL, health-related quality of life; HTAs, health technology assessments; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MCID, minimal clinically important difference; NASH, nonalcoholic steatohepatitis; PCPs, primary care physicians; SD, standard deviation; UK, United Kingdom; US, United States.

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Summary

- Health utilities measure how much society values a particular health condition and are used to help evaluate the costs and benefits of new treatments.
- We compared previously published health utilities with our real-world survey data for patients with a liver disease called metabolic dysfunction–associated steatohepatitis in France, Germany, Italy, Spain, the United Kingdom and the United States.
- We found that health utility values varied greatly across country scoring methods and differed from our real-world data, suggesting that country-specific scoring is needed which could help health authorities make decisions regarding treatment costs.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously nonalcoholic fatty liver disease [1] is a spectrum of chronic liver diseases. The most serious form of MASLD is metabolic dysfunction-associated steatohepatitis (MASH), previously nonalcoholic steatohepatitis (NASH), which can progress to hepatic fibrosis and cirrhosis or hepatocellular cancer in some individuals [2]. The overall global prevalence of MASLD has increased significantly in recent years and was estimated to be 37.8% for 2016 onwards in one meta-analysis [3]. MASH, especially at the more advanced stages, is also associated with comorbidities such as cardiovascular disease, obesity and type 2 diabetes [4]. This significantly impacts a patient's health-related quality of life (HRQoL) and places considerable strain on healthcare providers [5–9].

Measurement of HRQoL is a fundamental part of assessing the burden of a disease on an individual. The EQ-5D-5L questionnaire is a widely used, generic instrument that measures HRQoL outcomes in five dimensions [10]. The EQ-5D-5L can also be used to generate a single utility value that qualitatively describes a patient's overall health state, with values ranging from 1 (representing perfect health) to 0 (representing death) [11, 12]. Utility values are calculated based on responses to each of the five domains using country-specific tariffs that specify the societal value of the time individuals spend in any health state other than full health. Importantly, as health utility values are among the most influential elements associated with cost-effectiveness analyses, country-specific tariffs can have significant implications for which utility value to use. One study found that using different EQ-5D country tariffs on the same data resulted in substantially different incremental quality-adjusted life years estimates [13]. Specifically, the United Kingdom (UK) estimated values were approximately 1.5 times higher than those calculated using United States (US) or Danish tariffs in that study [13].

Furthermore, the EQ-5D is a preferred instrument in the health technology assessments (HTAs) used by agencies involved in reimbursement decisions to provide guidance on the use of new and existing medicines, products and treatments [14], including those conducted by the National Institute for Health and Care Excellence in the UK [15] and the Institute for Clinical and Economic Review in the US [16]. HTAs provide such agencies with a means of making comparisons across conditions and determining resource allocation, bearing in mind unlimited demands and increasingly limited budgets. Such comparisons need to be made in a condition-agnostic way, hence the use of measures like the health utility which also allows consideration of both length and quality of life in a single measure.

The aim of this study, which builds on a previous analysis that was presented at ISPOR 2023 [17], is to assess the reporting of EQ-5D utility values in existing MASH literature and to assess the validity of literature-reported values by comparing them with values with appropriate tariffs applied in matched cohorts from a large real-world survey of MASH patients.

2 | Methods

2.1 | Data Sources and Quality Control

2.1.1 | Literature Review

We performed a systematic literature review for publications reporting EQ-5D utility values in patients with MASH using the search terms described in Online resource 1 (Supplementary Methods; SM1 Table A). Electronic database (Embase, Medline and the Cochrane library) searches were conducted on May 5, 2022, to identify articles reporting health state utility values associated with MASH. The protocol-driven search strategies are described in Online resource 1 (Supplementary Methods; SM1 Table A). Manual searching of additional sources was also conducted. Using the publications identified in the systematic literature review, we followed the Professional Society for Health Economics and Outcomes Research (ISPOR) recommendations for extraction, review and synthesis of this information using the SPRUCE checklist for utility reporting [18] to guide the process, including the population, intervention, comparator and outcome (PICO) format, and relevant economic search terms such as utility, tariff and economic evaluations. To ensure the SLR output was up to date at the time of analysis, we conducted additional targeted searches to ensure all relevant papers were included.

2.1.2 | Disease Specific Programme (DSP) Data

Mean EQ-5D utility values identified in this literature search were compared with data from the Adelphi Real World NASH DSP, a cross-sectional survey with retrospective data collection conducted in France, Germany, Italy, Spain, the UK and the US between January and March 2019. The DSP includes a combination of abstracted physician-reported medical record data and patient-reported survey data. The full methodology of the DSP and its validation have been previously published [19–22], as well as its use in MASH [23].

Physicians included in the DSP were hepatologists, gastroenterologists, endocrinologists or primary care physicians (PCPs) personally responsible for managing and making treatment decisions for patients with MASH. Specialists were required to treat ≥10 patients with MASH per month, and PCPs were required to treat ≥5 patients with MASH per month.

Eligible physicians completed patient record forms for the next eight consconsulting patients with a physician-confirmed or suspected MASH diagnosis meeting predefined criteria. Patients were aged ≥18 years and were not involved in a MASH clinical trial at the time of data collection. Physicians reported information on demographics (including age, sex, ethnicity and body mass index) and clinical characteristics. The same patients were invited to complete a voluntary questionnaire that included the EQ-5D-5L, from which utilities were estimated by applying country-specific tariffs. These were completed independently of the physician immediately after consultation and were returned in a sealed envelope.

All responses were anonymised to preserve physician and patient confidentiality. Participating physicians and patients were assigned a study number to aid anonymous data collection and allow linkage of data during data collection and analysis. Data were de-identified and aggregated before receipt by Adelphi Real World.

2.2 | Statistical Analyses

After applying inclusion/exclusion criteria matched to each study identified in the literature to the DSP population, matching-adjusted indirect comparison analysis was used to balance DSP data with each of the literature-identified studies according to age, sex, comorbidities and fibrosis stage, as appropriate. Matching-adjusted indirect comparison analysis allows for comparison of data by re-weighting individual patient data from one study (in this case the DSP) to the baseline summary statistics of another (those sourced via the literature review), providing greater adjustment for observed differences compared with conventional meta-analytic methods [24]. Matching was undertaken separately and independently for each literature study. As a result, the demographic and clinical characteristics pertinent to each literature study were matched with the correct patient sample from the DSP database (Online resource 1; SM1 Table B). For example, when comparing the DSP data with data reported by Balp and colleagues [7], patients with hepatitis B/C or cirrhosis were excluded from the DSP in line with the inclusion criteria for that study, and matching was undertaken using age, sex and comorbid conditions (one or more heart or blood conditions, high blood pressure/hypertension and Charlson Comorbidity Index scores).

EQ-5D utilities were compared using weighted t-tests; two-sided *t*-tests were used where the standard deviation was reported in the literature, and one-sided t-tests were used where no standard deviation was reported. A minimal clinically important difference (MCID) between two utility values was defined as being >0.08 [25]. As the tariff used to score EQ-5D was not always reported in studies, the analysis was repeated using relevant country-specific EQ-5D scoring tariffs [26–31].

3 | Results

3.1 | Literature Review

Ten studies with varied recruitment criteria, patient demographics and clinical characteristics were identified in the literature review (Online resource 1; Supplementary Results; SM1 Table B) [7, 8, 32–40]. Study and patient characteristics for each study and also for the DSP are summarised in Table 1. Country-specific tariffs were either not used or the tariff used was not reported in the studies identified in the literature review. Those characteristics that were used in the matching process are shown in Online resource 1 (SM1 Table B).

Reported mean (standard deviation; SD) utility values are shown in Table 2. These ranged from 0.67 (SD not reported) [7] to 0.83 (0.14) [34] and 0.83 (0.21) [8]. Utilities from studies requiring a biopsy-confirmed MASH diagnosis ranged from 0.70 (SD not reported) [40] to 0.83 (0.14) [34]. Utilities from studies not requiring a biopsy-confirmed diagnosis ranged from 0.67 (SD not reported) [7] to 0.83 (0.21) [8].

3.2 | Matching-Adjusted Indirect Comparison of DSP and Literature Data

Comparisons of literature vs. DSP utility scores generated for France, Germany, Italy, Spain, the UK and the US using DSP data and national tariffs are shown in Table 2 and Figure 1.

DSP vs. *Balp 2019* (Figure 1A): Balp and colleagues reported an EQ-5D utility value of 0.67 for their survey of 184 patients with MASH from five European countries in the nationally representative National Health and Wellness Survey [7]. Patients with cirrhosis were excluded from participation. In total, 1239 DSP patients were included when the matching criteria shown in Online resource 1 (SM1 Table B) were applied. Using six tariffs for France, Germany, Italy, Spain, the UK and the US, six DSP EQ-5D utility values were generated. These ranged from 0.696 (SD 0.243) for the UK tariff to 0.856 (SD 0.176) for France, all of which were statistically significantly higher than the reported value of 0.67 (Table 2). Differences between the reported values and the DSP values only exceeded the MCID cut-off of 0.08 when the French, German and Italian tariffs were used.

DSP vs. *Cook 2019* (Figure 1B): In their survey, Cook and colleagues calculated EQ-5D utility scores for 166 MASH patients in Canada, Germany, the UK and the US [33]. The overall mean (SD) EQ-5D utility score for this patient cohort was 0.81 (0.17). The mean (SD) DSP values for 371 matched patients ranged from 0.739 (0.229) for the UK tariff to 0.887 (0.149) for France. Differences between the reported and the DSP utility values did not exceed the MCID. Differences did not achieve statistical significance when the Spanish and Italian tariffs were used (Table 2).

DSP vs. *Geier 2021* (Figure 1C): Geier and colleagues performed a cross-sectional analysis of data from 1216 participants in the Growth from Knowledge Disease Atlas Real-World Evidence programme [8]. Medical records data were provided by physicians in the US, France and Germany; participants also completed a survey that provided information on a range of aspects of their disease, including the EQ-5D. The mean (SD) utility value was 0.83 (0.21) in 299 patients, which was not clinically meaningfully different from values calculated for 1239 matched DSP patients (Table 2). Differences did not achieve statistical significance when the French and UK tariffs were used.

TABLE 1 | Overview of studies identified in the systematic literature review.

	Balp2019 [7]	Cook2019 [33]	Geier2021 [8]	O'Hara 2020 [39]	Ruiz2019[a] [40]	Younossi 2019 [36]	Younossi 2020 [32]	Younossi 2021a [35]	Younossi 2021b [34]	Younossi 2022 [38]	DSP data
Patients, *n*	184	166	1216	3754[b]	295	1667	1669	392	1679	1218	1280
Countries, *n* (%)[c]											
US	184 (100.0)	50 (30.1)	702 (57.7)	1221 (32.5)	NA	926 (55.5)	927 (55.5)	336 (85.7)	933 (55.6)	828 (68.0)	364 (28.4)
Canada	0 (0.0)	36 (21.7)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	NA	NA
France	0 (0.0)	0 (0.0)	227 (18.7)	508 (13.5)	NA	NA	NA	NA	NA	NA	156 (12.2)
Germany	0 (0.0)	50 (30.1)	287 (23.6)	540 (14.4)	NA	NA	NA	NA	NA	NA	340 (26.6)
Italy	0 (0.0)	0 (0.0)	0 (0.0)	540 (14.4)	NA	NA	NA	NA	NA	NA	120 (9.4)
Spain	0 (0.0)	0 (0.0)	0 (0.0)	522 (13.9)	NA	NA	NA	NA	NA	NA	198 (15.5)
UK	0 (0.0)	30 (18.1)	0 (0.0)	423 (11.3)	NA	NA	NA	NA	NA	NA	102 (8.0)
Countries not reported by study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	741 (45.5)	742 (45.5)	56 (14.3)	746 (44.4)	390 (32.0)	0 (0.0)
Mean age, years (SD)	54.5 (13.1)	52.0 (11.8)	54.9 (12.3)	53 (11.9)	NA	57.9 (8.8)	58 (9.0)	59.6 (9.0)	57.8 (8.9)	54.1 (11.5)	55.6 (11.4)
Sex, *n* (%)											
Male	105 (57.1)	8 (47.1)	699 (57.5)	2150 (57.3)	NA	673 (40.4)	673 (40.4)	139 (35.5)	679 (40.4)	524 (43.0)	756 (59.1)
Female	79 (42.9)	9 (52.9)	517 (42.5)	1604 (42.7)	NA	994 (59.6)	996 (59.7)	253 (64.5)	1000 (59.6)	694 (57.0)	524 (40.9)
Comorbidities, *n* (%)											
Hypertension	91 (49.5)	80 (48.2)	48.2	NA	NA	NA	NA	NA	NA	NA	656 (51.7)
Heart/blood conditions	127 (69.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	678 (53.4)

(Continues)

TABLE 1 | (Continued)

	Balp2019 [7]	Cook2019 [33]	Geier2021 [8]	O'Hara 2020 [39]	Ruiz2019[a] [40]	Younossi 2019 [36]	Younossi 2020 [32]	Younossi 2021a [35]	Younossi 2021b [34]	Younossi 2022 [38]	DSP data
T2DM	42 (22.8)	88 (53.0)	297 (59.2)[d]	(27)	NA	1232 (73.9)	1231 (73.8)	282 (71.9)	1237 (73.7)	663 (54.4)	729 (57.4)
Obesity	86 (46.7)	114 (68.7)	676 (55.6)	(35)	NA	NA	NA	NA	NA	NA	720 (56.7)
Depression	58 (31.5)	26 (15.7)	52 (10.4)[d]	(8)	NA	NA	431 (25.8)	NA	NA	NA	142 (11.2)
Dyslipidemia	NA	72 (43.4)	203 (40.4)[d]	(32)	NA	NA	NA	NA	NA	NA	589 (46.4)
Fibrosis stage, *n* (%)											
F0	NA	0 (0.0)	55 (7.0)	F0–2: 2604 (69.4)	35 (11.9)	NA	NA	0 (0.0)	0 (0.0)	0 (0.0)	127 (9.9)
F1	NA	0 (0.0)	175 (22.3)		71 (24.1)	NA	NA	0 (0.0)	0 (0.0)	287 (23.6)	343 (26.8)
F2	NA	106 (63.9)	278 (35.4)		75 (25.4)	NA	NA	0 (0.0)	0 (0.0)	411 (33.7)	208 (16.2)
F3	NA	60 (36.1)	211 (26.8)	F3 – F4: 1150 (30.6)	66 (22.4)	NA	801 (48.0)	171 (43.6)[e]	798 (47.5)	520 (42.7)	231 (18.0)
F4	NA	NA	47 (6.0)		48 (16.3)	NA	868 (52.0)	221 (56.4)	881 (52.5)	0 (0.0)	123 (9.6)
Unknown	NA	NA	20 (2.5)	NA	0 (0.0)	NA	NA	0 (0.0)	NA	0 (0.0)	248 (19.4)
Biopsy-confirmed MASH, *n* (%)	0 (0.0)	94 (56.6)	786 (64.6)	1619 (43.1)	295 (7.9)[b]	1667 (100.0)[f]	1669 (100.0)[f]	392 (100.0)[f]	1679 (100.0)[f]	1218 (100.0)[f]	653 (51.0)
Cirrhosis, *n* (%)	0 (0.0)	NA	NA	NA	NA	870 (52.2)	868 (52.0)	221 (56.4)	877 (52.2)	NA	NA
Compensated cirrhosis	0 (0.0)	NA	NA	NA	NA	NA	NA	221 (56.4)	NA	NA	407 (38.7)
Bridging fibrosis	NA	60 (36.1)	NA	NA	NA	797 (47.8)	638 (38.2)	171 (43.6)	802 (47.8)	NA	NA
Symptoms, *n* (%)											
Itch/fatigue	NA	25 (15.1)	NA	NA	NA	NA	447 (26.8)/539 (32.3)	NA	NA	NA	235 (18.5)
EQ-5D utility score, mean (SD)	0.67 (NA)	0.81 (0.17)	0.83 (0.21)	0.75 (0.26)	0.70 (NR)	0.827 (0.143)	0.828 (0.124)	0.809 (0.142)	0.831 (0.143)	0.814 (0.173)	0.768 (0.228)
Tariff used	NA	NA	NA	NA	NA	Crosswalk algorithm	NA	Crosswalk algorithm	Crosswalk algorithm	NA	Reported in Methods

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; NA, not available or not reported; *n*, number of patients; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[a]Country data not available due to the fact that pooled results were presented.
[b]Patient-reported outcomes data were only available for 749 patients.
[c]Based on $n = 502$ patients with available data recorded in medical records.
[d]Percentages may not add up to 10% depending on available data.
[e]Noncirrhotic disease (< F4).
[f]Data not reported, but the availability of liver biopsy was a study entry criterion.

TABLE 2 | EQ-5D values from the systematic literature review compared with those from matching-adjusted indirect comparison and country-specific tariffs.

	DSP patients		Literature population			
EQ-5D tariff	**Patients *n***	**EQ-5D, mean (SD)**	**Patients *n***	**EQ-5D mean (SD)**	**Difference**	***p***
Balp [7]	1239		184			
France		0.856 (0.176)			0.186	<0.001
Germany		0.809 (0.207)			0.139	<0.001
Italy		0.776 (0.245)		0.67 (NR)	0.106	<0.001
Spain		0.748 (0.219)			0.078	<0.001
UK		0.696 (0.243)			0.026	<0.001
US		0.714 (0.271)			0.044	<0.001
Cook [33]	371		166			
France		0.887 (0.149)			0.077	<0.001
Germany		0.846 (0.181)			0.036	0.025
Italy		0.819 (0.213)		0.81 (0.17)	0.009	0.583
Spain		0.788 (0.200)			−0.022	0.2
UK		0.739 (0.229)			−0.071	<0.001
US		0.766 (0.244)			−0.044	0.015
Geier [8]	1239		299			
France		0.893 (0.143)			0.063	<0.001
Germany		0.854 (0.175)			0.024	0.068
Italy		0.830 (0.202)		0.83 (0.21)	0	0.98
Spain		0.797 (0.195)			−0.033	0.014
UK		0.750 (0.223)			−0.08	<0.001
US		0.774 (0.237)			−0.056	<0.001
O'Hara [39]	3754		749[a]			
France		0.911 (0.136)			0.161	<0.001
Germany		0.878 (0.169)			0.128	<0.001
Italy		0.859 (0.190)		0.75 (0.26)	0.109	<0.001
Spain		0.833 (0.184)			0.083	<0.001
UK		0.787 (0.214)			0.037	0.001
US		0.815 (0.223)			0.065	<0.001
Ruiz [40]	553		295			
France		0.881 (0.154)			0.181	<0.001
Germany		0.837 (0.187)			0.137	<0.001
Italy		0.813 (0.206)		0.70 (NR)	0.113	<0.001
Spain		0.777 (0.196)			0.077	<0.001
UK		0.726 (0.225)			0.026	0.008
US		0.751 (0.237)			0.051	<0.001
Younossi 2019 [36]	250		1667			

(Continues)

TABLE 2 | (Continued)

	DSP patients		Literature population			
EQ-5D tariff	**Patients *n***	**EQ-5D, mean (SD)**	**Patients *n***	**EQ-5D mean (SD)**	**Difference**	***p***
France		0.855 (0.161)			0.028	0.01
Germany		0.809 (0.200)			−0.018	0.165
Italy		0.778 (0.229)			−0.049	0.001
Spain		0.752 (0.206)		0.827 (0.143)	−0.075	<0.001
UK		0.690 (0.249)			−0.137	<0.001
US		0.706 (0.266)			−0.121	<0.001
Younossi 2020 [32]	250		1669			
France		0.842 (0.135)			0.014	0.119
Germany		0.784 (0.172)			−0.044	<0.001
Italy		0.744 (0.185)			−0.084	<0.001
Spain		0.685 (0.157)		0.828 (0.124)	−0.143	<0.001
UK		0.631 (0.179)			−0.197	<0.001
US		0.647 (0.199)			−0.181	<0.001
Younossi 2021a [35]	855		392			
France		0.838 (0.205)			0.029	0.004
Germany		0.796 (0.243)			−0.013	0.24
Italy		0.761 (0.283)			−0.048	<0.001
Spain		0.742 (0.250)		0.809 (0.142)	−0.067	<0.001
UK		0.686 (0.290)			−0.123	<0.001
US		0.702 (0.308)			−0.107	<0.001
Younossi 2021b [34]	59		1679			
France		0.849 (0.188)			0.018	0.474
Germany		0.795 (0.236)			−0.036	0.246
Italy		0.767 (0.254)			−0.064	0.059
Spain		0.736 (0.240)		0.831 (0.143)	−0.095	0.004
UK		0.681 (0.277)			−0.15	<0.001
US		0.708 (0.283)			−0.123	0.002
Younossi 2022 [38]	778		1218			
France		0.876 (0.152)			0.062	<0.001
Germany		0.834 (0.181)			0.02	0.013
Italy		0.805 (0.214)			−0.009	0.35
Spain		0.775 (0.196)		0.814 (0.173)	−0.039	<0.001
UK		0.721 (0.227)			−0.093	<0.001
US		0.745 (0.245)			−0.069	<0.001

Abbreviations: DSP, Disease Specific Programme; *n*, number of patients; UK, United Kingdom; US, United States.
[a]Patients for whom patient-reported outcomes data were reported.

DSP vs. *O'Hara 2020* (Figure 1D): Using data from the retrospective, cross-sectional Global Assessment of the Impact of NASH (GAIN) study in France, Germany, Italy, Spain, the UK and the US, O'Hara and colleagues reported a mean (SD) utility value of 0.75 (0.26) in a cohort of 749 patients with EQ-5D data [39]. Mean (SD) EQ-5D utility values for 1027 matched DSP patients ranged from 0.787 (0.214) for the UK tariff to 0.911 (0.136) for France. Statistically significant and clinically meaningful

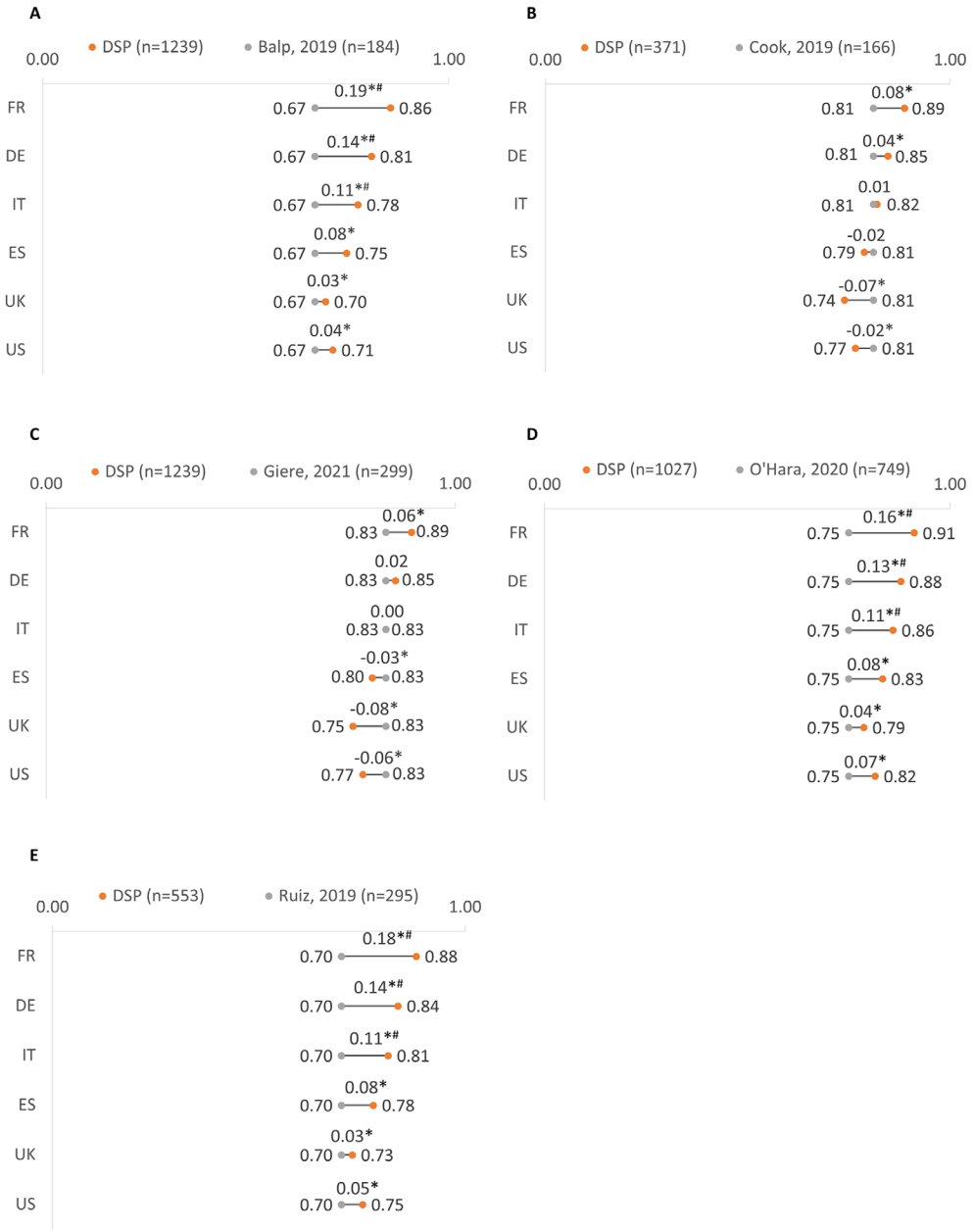

FIGURE 1 | Matching-adjusted indirect comparison of literature-reported and Disease Specific Programme EQ-5D utility scores: (A) Balp et al.; (B) Cook et al.; (C) Geier et al.; (D) O'Hara et al.; (E) Ruiz et al. *$p < 0.05$; #difference greater than minimal important clinical difference (0.08). DE, Germany; DSP, Disease Specific Programme; ES, Spain; FR, France; IT, Italy; *n*, number of patients; UK, United Kingdom; US, United States.

differences between the DSP and GAIN values were observed when French, German, Italian and Spanish tariffs were applied to the DSP data.

DSP vs. *Ruiz 2019* (Figure 1E): A subgroup analysis of the GAIN study identified 295 patients who had a liver biopsy and confirmed fibrosis score, for whom a mean EQ-5D utility value of 0.70 (SD not reported) was obtained [40]. In total, 553 DSP patients were matched with this patient cohort, and EQ-5D utility values of 0.726–0.881 were calculated using the six tariffs. Statistically significant and clinically meaningful differences were observed between DSP and reported values when the French, German and Italian tariffs were used with the DSP data.

Three separate analyses of patients with biopsy-confirmed F3 or F4 MASH who participated in the STELLAR phase 3 study have been reported by Younossi and colleagues [32, 34, 36]. As these analyses reported different baseline characteristics, each was matched separately with the DSP study, and application of the six tariffs resulted in different EQ-5D utility values.

DSP vs *Younossi 2019* (Figure 2A): In the first analysis of outcomes according to the extent of fibrosis, a mean (SD) utility value of 0.827 (0.143) was reported for 1667 patients [36]. Utility values ranged from 0.690 (0.249) for the UK tariff to 0.855 (0.161) for France for 250 matched DSP patients. These differences were only clinically meaningful and statistically significant when the UK and US tariffs were applied.

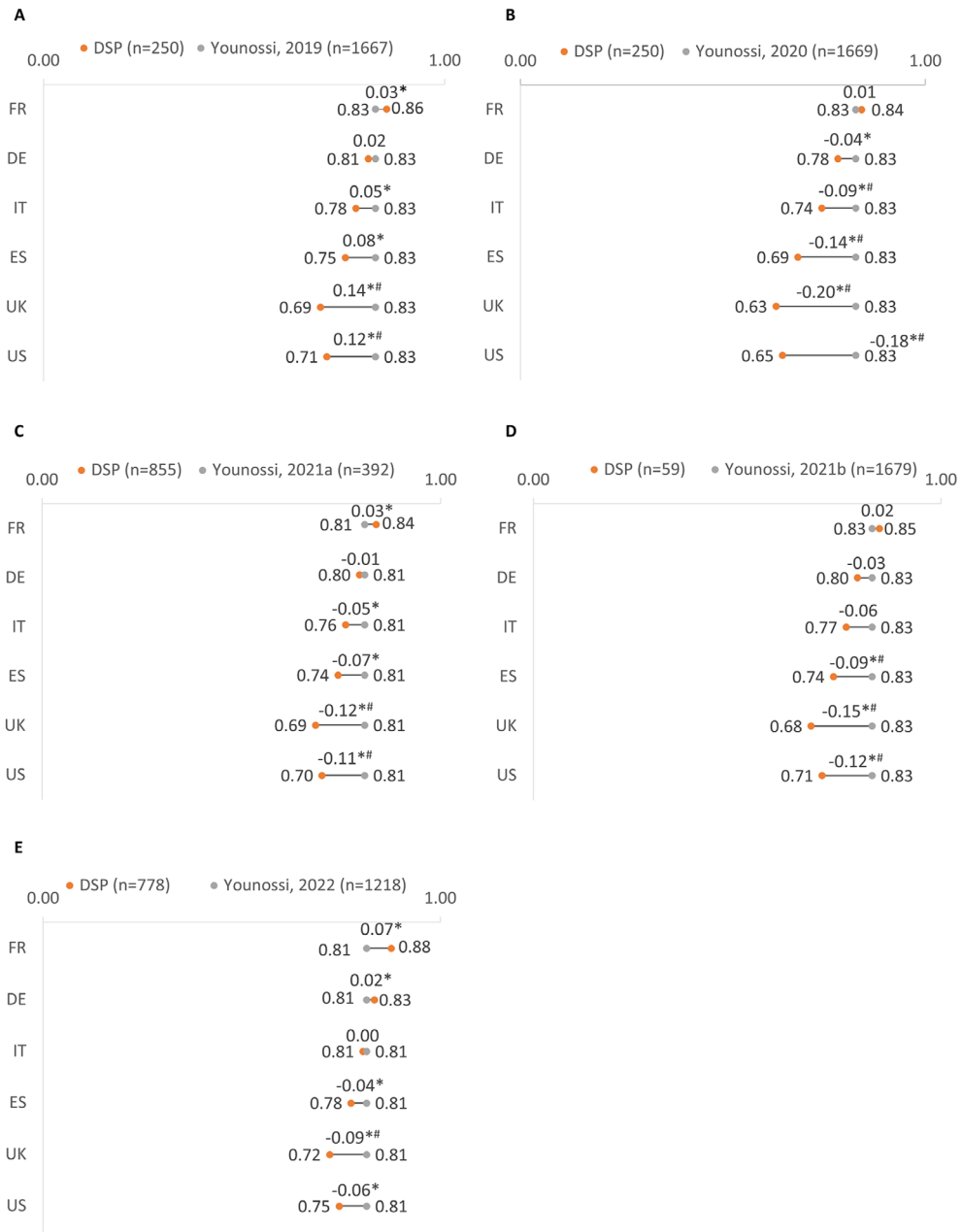

FIGURE 2 | Matching-adjusted indirect comparison of literature-reported and Disease Specific Programme EQ-5D utility scores: (A) Younossi et al. 2019; (B) Younossi et al. 2020; (C) Younossi et al. 2021a; (D) Younossi et al. 2021b; (E) Younossi et al. 2022. *$p < 0.05$; #difference greater than minimal important clinical difference (0.08). DE, Germany; DSP, Disease Specific Programme; ES, Spain; FR, France; IT, Italy; n, number of patients; UK, United Kingdom; US, United States.

DSP vs *Younossi 2020* (Figure 2B): The second analysis, which stratified 1669 patients according to the presence of fatigue and pruritis, reported a mean EQ-5D utility value of 0.828 (SD 0.124) in 1669 patients [32]. Among 250 matched DSP patients, mean (SD) utility values ranged from 0.631 (0.290) for the UK tariff to 0.842 (0.135) for France. Differences between utility values obtained using the Italian, Spanish, UK and US tariffs and the reported value were clinically meaningful and statistically significantly different (Table 2).

DSP vs. *Younossi 2021a* (Figure 2C): Younossi and colleagues also reported EQ-5D utility values for a group of 392 patients with F3 or F4 stage MASH in the randomised phase 2 ATLAS study [35]. The mean (SD) utility value in the ATLAS population was 0.809 (0.142). Matching identified 855 comparable patients in the DSP, for whom mean EQ-5D values ranged from 0.686 to 0.838, depending on the tariff applied; DSP values were lower than the reported value for all except the value obtained using the French tariff. The difference between the DSP value and the reported value was only clinically meaningful and statistically significant for the UK and US tariffs.

Younossi et al., 2021b vs *DSP* (Figure 2D): In the third report, utility values were reported according to noninvasive test results, with a mean (SD) value of 0.831 (0.143) for the overall population of 1679 patients [34]. Matching identified 59 comparable DSP patients, for

whom mean (SD) utility values ranging from 0.681 (0.277) for the UK to 0.849 (0.188) for France were calculated using the six tariffs. Differences were only clinically meaningful and statistically significant for the Spanish, UK and US tariffs.

DSP vs. *Younossi 2022* (Figure 2E): EQ-5D utility values were also reported for 1218 patients with MASH fibrosis stage F2 or F3, or F1 with at least one accompanying comorbidity, who participated in the phase 3 REGENERATE study [38]. The mean (SD) EQ-5D utility value for this patient cohort at baseline was 0.814 (0.173). Among 778 matched DSP patients, mean (SD) EQ-5D values ranged from 0.721 to 0.876, with the scores obtained using the Italian, Spanish, UK and US tariffs being lower than the reported value. Differences between DSP and reported values were clinically meaningful and statistically significant for the UK tariff alone.

4 | Discussion

Self-reported health as measured using the EQ-5D differs across countries as a result of different populations attributing varying degrees of value to the EQ-5D domains because of cultural, environmental and health system differences, among others [41, 42]. Country-specific EQ-5D tariffs or value sets were therefore developed to account for this, aiming to better inform decision-making by health authorities. We undertook this literature review and analysis to establish the extent to which country-specific tariffs have been used to date, and to highlight the effect different tariffs have on utility calculations. Ten studies describing EQ-5D utilities in patients with MASH were identified, and the methodological detail and patient characteristics reported in those studies were used to generate matched DSP samples. From these matched samples, utility values using six tariffs for France, Germany, Italy, Spain, the UK and the US were calculated. Two key findings emerged: firstly, EQ-5D utility values varied widely in literature studies, and secondly, country-specific tariffs were either not applied or not reported by the study authors.

The differences in reported utility values likely reflect the geographic, clinical and demographic characteristics of the populations included in the analyses. Balp and colleagues reported the lowest value of 0.67 in their analysis of HRQoL in European patients with MASH of all severities [7]. The highest value of 0.83 was reported by Younossi and colleagues in their analysis of the global STELLAR-3 and STELLAR-4 studies [34]. which included patients with MASH associated with cirrhosis and bridging fibrosis, and by Geier and colleagues in their analysis of the Growth from Knowledge Disease Atlas Real-World Evidence programme [8].

Our comparison of utility values generated from DSP data and country-specific tariffs with literature-reported studies highlighted statistically significant differences in many cases, as large sample sizes meant that small differences could nonetheless be statistically significant. In order to identify clinically meaningful differences, we used an MCID of 0.08 [25] in combination with statistical significance. For every study, there were at least two comparisons with a difference not exceeding the MCID of 0.08, indicating that the choice of tariff is important when deciding whether or not a set of derived results is different from those published. No clear pattern was observed in the direction of differences. DSP values were higher in some comparisons and when some tariffs were used, most notably the French tariff, and the literature-reported values were higher in other cases, most commonly the UK and US tariffs. This suggests that there was no systematic bias in DSP patient selection, where no liver biopsy or fibrosis inclusion/exclusion criteria are applied, suggesting that this might be considered a 'gold' or 'reference' standard of pseudo-random/convenience sampling, in which inclusion of the next 'n' patients gets closer to the 'true' mean.

It was not always apparent how EQ-5D utility values were derived in the reported studies. Only the studies reported by Younossi and colleagues stated that a crosswalk algorithm had been used in their analyses. In the interests of transparency and comparability of utility values obtained in patient populations in different countries with varying health systems, health expectations and cultures, we propose that future publications should include a detailed description of the tariff used to calculate utility values. The choice of tariff may substantially impact economic evaluation studies and funding decisions, as the use of different country-specific tariffs may lead to significant differences in derived utilities, quality-adjusted life years estimates and incremental cost-effectiveness ratios [13, 43, 44]. These three studies show that, across a range of indications, UK utilities, for example, tend to be lower for any given health state than US scores. Analyses of utilities for other diseases have also been shown to vary widely across countries, underscoring a need to be able to account for such differences [43, 45–49]. However, it is important not only to ensure that country-specific values are used but also to state which tariffs are being used, as studies using different tariffs cannot readily be compared [13]. Our findings, which showed statistically significant differences and, in some cases, differences exceeding clinically meaningful thresholds depending on the tariff used, are therefore not unsurprising.

This analysis of literature EQ-5D data and real-world values identifies the importance of considering a breadth of available evidence when reporting patient quality of life for HTA. The studies included in this literature review had different inclusion and exclusion criteria and other study design features, resulting in patient cohorts with varying disease characteristics, which would likely impact EQ-5D scores. The optimal approach, given these limitations, is to conduct a systematic review of published data such as we report. Our matching-adjusted indirect comparison of data from the DSP, a large and robust collection of information from patients routinely consulting in the real-world setting, provides further insight into HRQoL in this population of patients with MASH. An important element of the DSP process is the use of a consistent methodology and data capture from participants within and across countries, which results in internal consistency when comparing treatment patterns and outcomes across multiple regions [21].

This analysis has some limitations. Physicians are asked to provide data for a consecutive series of patients to avoid selection bias, but no formal patient selection verification procedures are in place. Additionally, MASH patients were identified based on the judgement of the respondent physician and not on a formalised diagnostic checklist. As such, patients did not have to be liver-biopsy confirmed MASH; however, this is representative of physician's real-world classification of patients. Where

comparisons were made to studies that required a liver biopsy, the data was filtered accordingly so only biopsy-confirmed patients were drawn from the DSP dataset. Some data, such as fibrosis stage, may be unknown due to testing performed by a previous treating physician, prior to the start of patient management by the physician reporting on the patients. It is important to consider the fact that weighted comparisons are only weighted to match the published data. There may be additional differences between the DSP and patients in a published study that cannot be matched if, for example, a desired characteristic has not been described in the publication or if a variable of interest was not captured in the DSP. Further, in using MAIC analysis here, patients are only weighted to match the means and proportions of the published data (as we cannot match the variability). With MAIC analysis, if there are few patients with a certain characteristic in the DSP sample, some patients may be given much larger weights than others and thus be classified as overly influential. Finally, to match the inclusion/exclusion criteria, some of our comparisons were made on reduced DSP samples as small as 59, which makes random variation in results more likely.

5 | Conclusions

In summary, the reporting of EQ-5D utilities is becoming more widespread in the MASH setting, but our analyses show published values can vary significantly depending on inclusion and exclusion criteria, sampling methodology and the country-specific EQ-5D tariff that was used in the calculation, which may lead to suboptimal reporting of patients' health status. Choosing an EQ-5D tariff appropriate for the study population is vital to obtain the clearest and most reliable patient-reported data and to achieve the most robust reporting.

Our analysis has shown the importance of these factors in estimating EQ-5D utilities that may ultimately be used in cost-effectiveness decisions and highlights the particular need for country-specific EQ-5D tariffs and sensitivity analyses in confirming the robustness of results and conclusions and informing effective decision-making by health authorities.

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Ethics Statement

The survey was performed in accordance with relevant guidelines and in line with the principles of the Declaration of Helsinki. As this was an analysis of secondary data, specific Institutional Review Board (IRB) approval was not required. However, the NASH DSP was submitted to Freiburger Ethik-Kommission International IRB (study code AG8065) in Europe and IRB approval was granted and to the Western IRB in the United States and an IRB exemption granted. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996 [51] and Health Information Technology for Economic and Clinical Health Act legislation [52].

Consent

All participants provided written informed consent to participate in the study. All participants provided written informed consent for use of their data including the publication of aggregated and deidentified data.

Conflicts of Interest

James Piercy, Victoria Higgins and James Pike are employed by Adelphi Real World. Jesse Fishman was employed by Madrigal Pharmaceuticals at time of writing and is now an independent consultant.

Data Availability Statement

All data, i.e., methodology, materials, data and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Victoria Higgins at victoria.higgins@adelphigroup.com. Victoria Higgins is an employee of Adelphi Real World.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.