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The Cost of Diagnosing and Managing Non-Alcoholic Steatohepatitis in Europe and the United States

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ABSTRACT

Background & Aims: Non-alcoholic steatohepatitis (NASH) is acknowledged as a severe disease that is associated with a significant burden on patients, payers, and society. However, limited evidence exists on the cost associated with NASH across different countries. This analysis aims to describe the cost associated with the routine care of patients with NASH in France, Germany, and the United States.

Methods: Data was sourced from the Gesellschaft für Konsumforschung (now Ipsos) Disease Atlas Real-World Evidence program collected from July through November 2017 in France, Germany, and the United States. Country-level unit cost was estimated from national databases for diagnostic tests and procedures, prescription drugs, hospital stays, and outpatient visits in respective local currency based on 2017 values. These were combined to provide an estimate of the cost of management of confirmed NASH in this specific patient population and are presented as mean cost per patient per year for each country in local currency and as USD adjusted for purchasing power parity for comparison.

Results: Annual mean ± standard deviation cost of non-alcoholic steatohepatitis ranged from purchasing power parity USD 1,049±2,461 in Germany to USD 1,723±2,988 in the United States. In all markets, the predominant contributor to cost is healthcare resource use represented by hospitalisation and outpatient visits.

Conclusions: This study reveals that costs associated with NASH treatment and management vary across the three countries studied, in part due to differences in healthcare systems but also due to different approaches in managing this disease. Our analysis represents the costs for a specific cohort of patients and further studies are warranted to better understand the progressive impact of NASH on healthcare systems and society.

Key words: non-alcoholic steatohepatitis – cost of illness – healthcare resource utilisation – non-alcoholic fatty liver disease.

Abbreviations: AASLD: American Association for the Study of Liver Diseases; GLP-1 RA: glucagon-like peptide-1 receptor agonists; HRU: healthcare resource utilization; NAFL: non-alcoholic fatty liver; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; UDCA: ursodeoxycholic acid.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of chronic liver diseases notably simple fatty liver (hepatic steatosis) referred to as non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) [1]. Non-alcoholic fatty liver is often diagnosed late usually as a result of a combination of factors such as the nonspecific nature of symptoms, lack of awareness by providers and patients, and insufficient screening [2-4]. Currently, liver biopsy is the gold standard to confirm the diagnosis of NASH but is only recommended for patients that are at high risk for advanced disease and may benefit from therapeutic intervention. Liver biopsy is not available for broader applicability for many reasons, including potential risk, the expense and expertise required for histological interpretation [1]. Current estimates suggest that 25% of the global population has NAFLD and of these, 20–25% will go on to develop NASH [5], therefore representing a significant burden to healthcare systems. In addition, NASH patients are frequently obese and have significant metabolic comorbidities such as hyperlipidemia and type II diabetes [6]. The risk that NASH progresses to

cirrhosis, liver cancer, liver failure, and ultimately death, is increased the longer the condition remains untreated [7], and NASH is currently the second leading indication for liver transplantation in the United States and a leading indication in other parts of the world [8, 9].

Despite the increasing number of patients with NASH and NASH-related cirrhosis, there remains a clear lack of treatment options. Current management of NASH is frequently based around lifestyle modifications that include exercise and dietary modifications to reduce calorie intake, given there is currently no approved treatment [1]. The American Association for the Study of Liver Diseases (AASLD) advises that the management of NASH should consist of treating liver disease and the underlying co-morbidities such as obesity, insulin resistance, type II diabetes and hyperlipidemia [1]. Therefore, many patients with NASH require a diverse range of medications for the associated co-morbidities, as well as frequent healthcare visits and monitoring. The increasing prevalence of NASH has implications on healthcare resource utilisation (HRU) for management of patients, particularly given the lack of approved treatments with the exception of liver transplantation.

It is estimated that the annual healthcare cost associated with NAFLD in the United States in 2016 was approximately USD103 billion, and €35 billion in four European countries combined (Germany, Italy, United Kingdom and France) [5]. The largest increases in HRU which may account for increased costs in NAFLD when compared with matched controls with similar comorbidities are liver biopsies and hospitalizations [10]. However, the economic burden of NASH specifically is poorly documented with few studies to date investigating the real economic impact of patients with NASH, both to society and to the patients themselves [11]. A recent study captured real world evidence on the economic burden of NASH, revealing a substantial burden on health services and patients, with a per patient cost of NASH shown to be the highest in the United States and the lowest in France [12]. Even more recently, another study providing a cost of illness analysis in five European markets has concluded that the majority of economic and wellbeing costs of NASH are experienced in the later stages of the disease [13]. Here, the overall aim of our study is to further contribute to the understanding of the economic burden posed by NASH in France, Germany and the US.

METHODS

Study Design and Population

This study used data from the GfK Disease Atlas Real-World Evidence (NASH-Atlas) program, which applied a non-interventional, retrospective, observational, cross-sectional study design. Data was collected from July through November 2017. Physicians managing NASH patients in France, Germany, and the United States took part in the study if they met a minimum set of inclusion criteria, published previously [14]. Data from medical records of their next 5–10 eligible NASH patients were reported by physicians via an online interface. Full details of inclusion and exclusion criteria have been previously published [14]. Physician and patient numbers included in the study are shown in Supplementary Table I.

Direct Costs Analyses

Direct medical resources included in this analysis were selected diagnostic tests and procedures (liver biopsy, ultrasound, computed tomography and magnetic resonance imaging scans, transient elastography, aspartate aminotransferase, alanine aminotrasferase and gamma-glutamyl transpeptidase levels, lipid profiling, platelet count, and clotting studies) and pharmaceuticals used in the management of patients with NASH. Additionally, costs for routine medical visits and hospitalization were incorporated.

Cost Estimations

Country-level unit cost was estimated from national databases for each identified resource in respective local currency based on 2017 values. Costs for diagnostic tests and procedures, and medical visits were sourced from Ameli (France), Einheitlicher Bewertungsmaßstab (EBM) (Germany) and Medicare (The Medicare Physician Fee Schedule (2017); Clinical Diagnostic Laboratory Fee Schedule (2017) (US).

The mean cost per patient per year for diagnostic tests and procedures was calculated by multiplying the unit cost for each test/procedure (Supplementary Table II) by the number of tests conducted. Test frequency and percentage of patients receiving each test were previously published [14] and can also be found in Supplementary Table III (presented as mean number per patient per year across the relevant cohort/ by country).

Pharmaceutical prices were sourced from eVidal (retail price), Lauer (retail price) and Analysource (wholesale acquisition cost) for France, Germany and the US, respectively.

Pharmaceuticals included were based on the physicans' stated answers to medication prescribed for each patient based on a predetermined selection of treatments, cognizant that at present there are no approved treatments for NASH: Total annual mean cost of diagnostic tests and procedures per patient, by country. Annual treatment costs were calculated as the median of available drugs within each class; dose was based on dosing information according to the defined daily dose (DDD) by the World Health Organization (WHO). For France, 65% of the retail price including value-added tax (prix public toutes taxes comprises PPTTC) was used based on the usual reimbursement rate. For Germany, a simplified reimbursement rate was calculated using the retail price with the published discount levels applicable to originator and generic prices. The median annual treatment costs for the pharmaceutical treatments included in this analysis can be found in Supplementary Table IV.

In France and Germany, the cost for a hospital stay was calculated using the WHO data for the cost of inpatient curative care, Eurostat for total hospital beds and Organization for Economic Co-operation and Development (OECD) Health Statistics (2019) for occupancy rate of curative bed days to calculate the average cost per night. Costs for an overnight stay in hospital in the US were calculated using WHO data for the cost of inpatient curative care and Healthcare Cost and Utilization Project data for inpatient stays and duration to calculate the average cost per night. The sum of the average number of nights as stated by the physicians for inpatient and Intensive Care Unit (ICU) stays was multiplied by the average cost per night as stated above.

After estimating the cost of each identified resource, the total annual cost per patient per country was calculated. For better comparability, the total costs reported for France and Germany (both in EUR) were converted into purchasing power parity (PPP) US dollars (USD) of 2017 using PPP exchange rates (0.770 EUR/PPP USD(2017) and 0.745 EUR/PPP USD(2017), respectively) as reported by the OECD [15].

RESULTS

Key characteristics of the patient profile for this cohort of 1,209 patients, 226 patients from France, 285 patients from Germany, and 698 patients from the US, is shown in Table I. It includes 45.8%, 64.5% and 70.8% of patients who had their NASH diagnosis confirmed by biopsy in France, Germany and the US, respectively. The mean time patients with NASH had been under physician care for this condition was 27±40.1, 25.7±27.5 and 27±40.2 months in France, Germany and the US, respectively. Full details of patient demographics and clinical profiles have been reported previously [14]. The patients in each country had a fibrosis level reported by their physician with less than a third having advanced disease (Table I).

Direct Medical Costs

The mean ± standard deviation annual costs for diagnosing NASH and monitoring disease progression are shown in Table II. Unit costs for each of these diagnostic tests, which include common blood tests, imaging and radiography tests, are shown in Supplementary Table II.

Table I. Patient demographics and medical characteristics, by country

	France	Germany	US
Patients, n	226	285	698
Patient demographics			
Age, years (SD)	56.9 (12.9)	56.9 (10.3)	53.5 (12.6)
Male, %	65	59	55
Female, %	35	41	45
Stage of disease			
Early fibrosis stage, n (%) (F0, F1, F2)	138 (61)	174 (61)	412 (59)
Advanced fibrosis stage, n (%) (F3, F4)	59 (26)	69 (24)	175 (25)
Unknown stage of fibrosis, n (%)	29 (13)	42 (14)	111 (16)
On waiting list for liver transplant, n (%)	4 (2)	10 (3)	30 (4)
Most common co-morbidities			
Patients for whom co-morbidities were reported by physician, n	95	128	279
Type 2 Diabetes, n (%)	56 (59)	79 (62)	162 (58)
Hypertension, n (%)	44 (46)	68 (53)	130 (47)
Obesity, n (%)	24 (25)	65 (51)	150 (54)
Dyslipidaemia, n (%)	27 (28)	52 (41)	124 (44)
Metabolic syndrome, n (%)	23 (24)	30 (23)	55 (20)

SD: standard deviation.

Table II. Total annual mean cost of diagnostic tests and procedures per patient, by country

	France	Germany	US
Patients, n	226	285	698
Mean cost per patient per year (SD)	€210.21 (€157.55)	€186.96 (€218.91)	$590.44 ($507.69)

SD: standard deviation.

Utilization rates of pharmaceutical treatments in each cohort and annual per patient costs for the pharmaceutical management of NASH are shown in Table III. Differences between markets in the management of NASH are apparent, with clinicians in the US and Germany favoring metformin and statins while clinicians in France prescribed ursodeoxycholic acid (UDCA) more frequently.

Table III. Utilization rates of pharmaceutical treatments and total annual mean cost of pharmaceutical management of NASH per patient, by country

	France	Germany	US
Patients, n	226	285	698
Utilization rate of pharmaceutical treatments			
Pioglitazone, %	N/A*	N/A*	9
Metformin, %	19	26	18
GLP-1 RA (exenatide, liraglutide), %	3	9	2
Ursodeoxycholic acid, %	22	9	5
Statins, %	15	27	27
Fenofibrate, %	6	4	4
Cost of pharmaceutical management of NASH			
Mean cost per patient per year (SD)	€106.16 (€191.73)	€291.53 (€529.42)	$458.62 ($1,429.82)

GLP-1 RA: glucagon-like peptide-1 receptor agonist N/A: not applicable; *: withdrawn from market.

The cost of healthcare resource utilization was based on information collected on the number of medical visits and the number of nights in hospital (including the number of nights in ICU). Total annual mean cost of medical visits and hospitalization per patient is shown in Table IV.

Table IV. Total annual mean cost of NASH-related hospitalisation and medical visits per patient, by country

	France	Germany	US
Patients for whom outpatient visits were reported by physician, n	226	285	698
Mean number of outpatient visits per year (SD)	4.59 (3.73)	4.61 (3.43)	3.96 (2.63)
Patients for whom hospital stays were reported by physician, n	210	265	687
Mean number of days in hospital per year (SD)	0.85 (4.12)	0.34 (2.70)	0.11 (0.69)
Total mean cost per patient per year (SD)	€839.58 (€3,657.56)	€302.79 (€1,650.21)	$673.78 ($2,384.68)

SD: standard deviation.

Overall Comparative Costs

The combined annual costs of diagnostic and monitoring tests, prescription drugs, medical visits, and hospital stays per patient with NASH are shown in Table V. Local currency units have been converted to PPP USD for cross comparison between markets. Healthcare costs for the management of patients with NASH are highest in the US and lowest in Germany.

Table V. Total annual mean cost of NASH per patient, by country

	France	Germany	US
Total mean cost per patient per year (SD) [LCU]	1,156 (3,700)	781 (1,834)	1,723 (2,988)
Total mean cost per patient per year (SD) [PPP USD (2017)]	1,501 (4,805)	1,049 (2,461)	1,723 (2,988)

LCU: local currency unit; SD: standard deviation.

DISCUSSION

The aim of this study was to broaden the understanding of the economic impact associated with the diagnosis and management of patients with NASH in France, Germany and the US. The study complements the knowledge base from other studies that have investigated the healthcare costs associated with treating and managing patients with NASH in European markets (France, Germany, Italy, Spain, and the United Kingdom (UK)) and the US [12, 13]. One key finding from this study is that costs associated with diagnosis and management of patients with NASH are not uniform across countries. Diagnostic and managements costs in the US are higher than those in France and Germany. The difference in the costing of the management of NASH may reflect differences in healthcare systems and reimbursement policies for diagnostic tests, which can impact treatment patterns and behaviors, such as more frequent testing and increased utilization of liver biopsies in the US. Given the similarities between the national cohorts with respect to the stage of fibrosis, it is likely that the differences in cost are not driven by this factor.

In this cohort of patients, which represents a snapshot in time of patients that have been under physician management for an average of over 2 years, the cost drivers for the management of NASH in all markets were hospitalization and medical visits. Hospitalization costs illustrated in this study apply an average daily rate for a hospital stay multiplied by number of days in hospital. However, this may provide an incorrect estimate of the overall HRU given that it is unclear for which specific procedures a patient may have been hospitalized, if the nights in hospital were multiple isolated nights, or extended hospital stays – all factors which affect the ultimate cost associated with hospitalization. Additional underrepresentation may also be driven by the lack of inclusion of surgical costs and liver transplantation. In this cohort, between 2 to 4% of patients were placed on a waiting list for a liver transplant, which would ultimately result in additional HRU costs from the transplantation and management. Given that this cohort predominantly consists of patients in early stages of the disease, it can be hypothesized that with disease advancement to end stage liver disease, the number of patients requiring a liver transplant would increase with a subsequent increase in associated HRU costs.

Diagnostic costs are primarily driven by liver biopsy costs, which is not unexpected given 65% of patients in this cohort had received a liver biopsy. While this may lead to a slight over-representation of annual procedure costs in our study, it should be noted a liver biopsy remains the only reliable procedure and is considered the reference standard for a confirmatory NASH diagnosis. If future treatments in development for NASH are to be reserved for those patients with a confirmed diagnosis, the costs associated with diagnostic testing are likely to increase without the development of a cheaper, less invasive but reliable diagnostic option.

There are limited pharmacological interventions for the treatment of patients with NASH and as such, many patients are treated for their co-morbidities in a bid to have a positive effect on NASH itself. The five most common co-morbidities were the same in all three countries, suggesting that the choice of pharmacological interventions and, consequently, their cost are reflective of differences in treatment strategies between countries. Moreover, the cost varies across markets representative of differences in the disease's clinical management protocols. In Germany, and the US, the cost of drugs is primarily driven by glucagon-like peptide-1 receptor agonists (GLP-1 RA) in contrast with France, where UDCA accounts for the greatest drug costs (Supplementary Table IV). While pioglitazone accounts for a significant treatment cost in the US, this drug is no longer marketed in France or Germany. Overall, treatment costs estimated for the cohort in this study represent a relatively small proportion of the total cost of NASH management. However, we did not capture any drugs to treat any of the potential presentations of late-stage NASH which have been shown to be more costly [13]. However, it should be noted that additional out of pocket costs for drugs and supplements not necessarily reimbursed by health authorities, such as vitamin E, vitamin D, and omega-3-fatty acids, all of which are available as over-the-counter products, may add further economic burden to the patient or healthcare system, if these are prescribed by the physician.

Previous studies have also investigated the economic burden presented by NASH in similar markets to our study. One such study by O'Hara et al. [12] estimated the direct medical costs, direct non-medical costs and indirect costs associated with NASH from patients in France, Germany, Italy, Spain, and the UK. Similar to our study, their approach was to gain input from physicians and patients on clinical and economic data before estimating costs attributable to this data. Whilst our overall direct costs differ when considered in comparison, this is most likely representative of the differing elements included in "direct medical costs". The study by O'Hara et al. [12] includes surgery costs, a category not considered in this analysis. When considering isolated elements of the direct costs, similar costs for procedures and tests in both France (€210 vs. €124) and Germany (€186 vs. €183) are reported. Costs of drug treatment differ between the two studies, which is likely a reflection of differing treatments included in the cost calculation. In our study, we specifically include costs for pioglitazone, metformin, GLP-1 RA, UDCA, statins and fenofibrate as indicated in Table

III. However, it is unclear which specific drugs were included in the study by O'Hara et al. [12]. Nevertheless, both studies clearly highlight the differing costs attached to management of NASH, which is reflective of non-standardized treatment approaches, both within and across markets.

An additional economic study, a cost of illness study, in five European markets (France, Germany, Italy, Spain, and the UK) was recently undertaken by Schattenberg et al. [13] and modeled the socioeconomic burden of NASH using a literature review, databases, and clinical expert opinion. This study showed that the cost of NASH was greater in those patients in the later stage of disease. Our study was assessing a cohort of patients that is predominantly in the early stages of disease (F0-F2) and therefore represents a differing cost. Moreover, our study assessed the cost per patient, compared to the Schattenberg et al. [13] analysis where the focus was the overall cost to the healthcare system. Therefore, the results from our study are not directly comparable. However, in agreement with our findings, cost variations between markets are influenced by the differences in approach of diagnosis and monitoring of patients with NASH, further confirming a lack of consistency in patient management [13].

Given the high proportion of patients undergoing liver biopsy, we should note that the patient cohort in this study may not be fully representative of the overall population of patients with NASH, and only reflects the cost incurred in this specific cohort with diagnosed NASH. It is not to be extrapolated to the entire fatty liver population but could be extrapolated to other diagnosed NASH patients. Furthermore, we also note that annual costs might not be stable and may decline over time, particularly in patients who are in the early stages of the disease and patients with slow disease progression.

The economic impact of NASH is significant as it mirrors the growing prevalence in obesity and other metabolic syndrome related comorbidities, predisposing risk factors to NASH development. Understanding the cost of NASH is complex given the lack of standardised treatment practices across countries, and the fact that there is no "standard" NASH patient. Our results reflect the annual cost per patient from a cohort that had been under management for over 2 years, biased towards those that had received biopsies and predominantly with early stage disease (F scores of F0–F2). Other studies discussed have reported costs for patient cohorts with slightly different characteristics, leading to differing cost estimations. Across all the currently published economic studies, it is likely that the cost of diagnosis and management of NASH remains underestimated, as to date no single study has captured all elements of diagnosis and management. It would be interesting to understand within a single study how costs vary according to disease severity, in order to understand if earlier diagnosis and treatment can prevent later line costs. Given the anticipated increase in the prevalence of NASH in the future, understanding the economic burden both to the healthcare systems and to society will be important.

CONCLUSIONS

This study provides further evidence to that already published in understanding the economic burden of NASH. Moreover, given the particular patient characteristics in this cohort, it further demonstrates the need to better understand the various endotypes of NASH patient, if such a classification is possible.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-4275

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Authors' contributions: A.G., S.H., R.H., A.C.S., M.R. and V.R. analyzed and interpreted the data, and drafted the manuscript. M.M.B. was involved in designing the study, interpreting the data and drafting the manuscript. C.B., M.P., J.C. were involved in interpreting the data. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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