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ORIGINAL ARTICLE

The humanistic burden associated with caring for patients with advanced non-small cell lung cancer (NSCLC) in three European countries—a real-world survey of caregivers

R. Wood[1] · G. Taylor-Stokes[1] · M. Lees[2]

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Abstract

Purpose This study evaluated the humanistic burden on caregivers of patients with advanced non-small cell lung cancer (aNSCLC) as the disease progresses.

Methods Data were drawn from a cross-sectional study of patients with aNSCLC and their caregivers conducted in France, Germany, and Italy between 2015 and 2016. Data were collected by medical chart review and patient and caregiver questionnaires. The EuroQol five-dimension three-level (EQ-5D-3L) was used to evaluate patient and caregiver health status. Caregivers also completed the Work Productivity and Activity Impairment (WPAI) questionnaire and Zarit Burden Interview (ZBI).

Results The population for the analysis consisted of 427 caregivers (mean age 53.5 years; 72.6% female; 54.9% spouse; 36.2% in full-time employment) and 427 matched patients (mean age 66.2 years; 68.6% male). Most (69.5%) patients were receiving first-line therapy for advanced disease. Patients' caregivers provided a mean of 29.5 h of support per week. Significant differences in EQ-5D-3L scores were observed between caregivers of patients receiving first and later lines of therapy in France (0.87 vs. 0.78; $p = 0.0055$). Among employed caregivers, overall work impairment was considerable and ranged from 21.1% in Germany to 30.4% in France and 29.7% in Italy. Caregivers of patients receiving later lines of therapy in France rated their own health status as significantly worse than did those caring for patients receiving first-line therapy (82.7 vs. 72.9; $p = 0.0039$).

Conclusions Informal caregivers provided the majority of support for patients with advanced NSCLC and their caregiving activities impose a significant humanistic burden.

Keywords Caregiver burden · Lung cancer · Quality of life · Work productivity · Anxiety · Depression

Introduction

Lung cancer is the leading cause of cancer-related deaths in Europe, accounting for approximately 20% of all such deaths [1]. Around 400,000 new cases of lung cancer are diagnosed in Europe each year [2], of which the majority, around 85%, are non-small lung cell cancer (NSCLC; [3, 4]). Diagnosis, disease treatment, and the associated side effects impose a significant psychological, emotional, and financial burden for patients [5–12].

Informal (unpaid) caregivers play a crucial role in supporting patients with chronic and life-threatening or life-limiting disease, a role with both positive and negative implications for their own health state and emotional well-being [13–15]. Without caregiver support, the care would need to be provided by the healthcare system or social care system. Caregivers of patients with NSCLC often experience psychological and emotional distress, disruption of daily routines, and financial hardship as a result of their caregiving responsibilities [5, 6, 9, 16–18]. The limited number of studies in this area has focused on the quality of life (QoL) and emotional burden of caring for a patient with lung cancer [9, 16, 18]. In 2017, Borges et al. reported the results of a prospective, cross-sectional study among patients with lung cancer and their caregivers [5]. Using the Caregiver Burden Scale, they found an association between increasing caregivers' perceived burden, QoL, and levels of anxiety and depression and patients decreasing QoL, regardless of disease stage [5]. This critical

✉ R. Wood
robert.wood@adelphigroup.com

[1] Adelphi Real World, Bollington, UK

[2] Bristol-Myers Squibb, Rueil-Malmaison, Paris, France

observation highlights the increasing burden on caregivers as the patient's disease and their symptoms progress and their life quality declines. Despite the burden on caregivers, they can also experience a sense of satisfaction from their caregiving activities [14].

There is limited information on the humanistic burden incurred by caregivers of patients with advanced NSCLC. Humanistic burden is a concept that encompasses the total impact of a state or condition including emotional, life quality, social, interpersonal, health, and productivity aspects with the aim of capturing a holistic overview of the experienced burden. Moreover, there have been no systematic evaluations of the type of care the caregivers provide and the responsibilities they assume. Cultural and policy differences among European countries are known to impact end-of-life care and caregiving practices [19–22]. For this reason, the current research was conducted across Germany, Italy, and France in order to capture differences in cultural values, healthcare practices, and levels of formal caregiver support. The aim of the current research was to quantify the humanistic burden associated with advanced NSCLC from a caregiver's perspective, including caregiver QoL, across the three European countries.

Methods

Data were drawn from a multi-center, cross-sectional study of patients with stage IIIB or IV NSCLC and their caregivers conducted in France, Germany, and Italy. Data were collected between May 2015 and June 2016 via a medical chart review, a patient questionnaire, and a caregiver questionnaire. All data were fully de-identified, collated and aggregated, and coded to permit linkage between physician-reported data, patient-reported outcomes, and their caregiver responses.

Participating physicians invited patients with advanced NSCLC and their accompanying caregivers to take part in the study. A combined information sheet and informed consent form fronted both the patient and caregiver paper questionnaires. Patients and caregivers received an information sheet highlighting the following: the objectives of the study; that completion of the questionnaire was entirely voluntary; that they were free to withdraw at any point; and assurances that any responses they gave would remain confidential. Patient and caregiver informed consent was confirmed by an anonymized tick box on the front page of the paper questionnaire distributed by the consulting physician. Patients and/or caregivers, who did not wish to participate, did not complete a questionnaire and were not included in the study.

Inclusion criteria

Patients (male or female, ≥ 18 years of age) were eligible to participate if they had histologically or cytologically confirmed stage IIIB or IV NSCLC and had initiated their first therapy for advanced NSCLC at least one calendar month prior to data collection. Accompanying caregivers (adults, ≥ 18 years of age) were eligible to participate if they were a primary caregiver providing informal (unpaid) care for the patient. Patients participating in a clinical trial at the time of this research were not eligible to participate, nor were their accompanying caregivers. The study protocol was approved by a central Institutional Review Board (Freiburg Ethics Commission International—Ref 015/1196).

Data collection

Patient report forms were completed by the treating physician with data drawn from the medical record. Data collected included demographics (age, sex, smoking history), disease characteristics (including stage and presence of brain metastases), and current line and type of treatment.

The caregiver self-completion questionnaire collected data on demographics (age, sex, relationship to patient), support provided (type, time spent providing support other carers), and impact on caregiver (health, treatment required as a consequence of caregiving). Caregivers also completed the EuroQol five-dimensional questionnaire three-level version (EQ-5D-3L; [23]), the Zarit Burden Interview (ZBI; [24]), and the Work Productivity and Activity Impairment Questionnaire General Health version (WPAI: GH; [25]). The EQ-5D is a validated and standardized instrument for the measurement of general health status. Five general (non-disease-specific) health dimensions are evaluated (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The three-level version assesses each item as "having no problems," "some or moderate problems," or "unable to do/having extreme problems." An index score is calculated, whereby 1 is perfect health, 0 is death, and < 0 is a state worse than death. The questionnaire also includes a visual analogue scale (VAS) through which the patients rate their own perceived health status on a vertical scale from "best imaginable health state" (100) to "worst imaginable health state" (0). The ZBI is a 22-item scale initially designed to measure feelings of burden experienced by caregivers of elderly persons with dementia and now used to measure feeling of burden among caregivers for patients with a range of conditions. Caregivers were asked to respond to questions about the impact of the patient's disabilities on their life. The ZBI total score ranges from 0 (no burden) to 88 (severe burden). Caregivers with ZBI total scores of ≥ 24 were considered to be at risk of depression [26]. The WPAI-GH consists of six items covering employment status, hours missed from work due to health problems, hours missed from work due to other reasons, hours actually worked, and a further two questions that measure the extent to which health problems affected productivity while working and the ability to do regular activities. Four domains are

derived, whereby higher scores are indicative of higher levels of impairment.

Statistical analysis

Analyses were conducted on data drawn from 427 matched patient and caregiver forms and were stratified by country and by patients' line of therapy (first line vs. second line or later). Descriptive statistics are presented throughout. Statistical significance was assessed using Mann-Whitney *U* and Fisher's exact tests for numeric and nominal outcomes, respectively. All statistical tests performed were two-sided in nature and a significance level of 0.05 was used. Missing data was not imputed and thus remained missing. All analysis was performed in Stata 14 software [27].

Results

A total of 141 physicians participating in the study agreed to recruit patients and their accompanying caregivers on behalf of the research team (France $n = 43$ [30.5%], Germany $n = 50$ [35.5%], Italy $n = 48$ [34.0%]). Overall, 1030 consulting patients and 427 accompanying informal caregivers were recruited. The population for this analysis consisted of 427 caregivers (France $n = 148$ [34.7%]; Germany $n = 150$ [35.1%]; Italy $n = 129$ [30.2%]) and 427 matched patients.

Caregiver mean age (standard deviation [SD]) was 53.5 (12.5) years; 72.6% were female and most were either the patient's partner/spouse (54.9%) or child (31.9%) (Table 1). The mean age of patients was 66.2 (SD 9.5) years; 68.6% were male, 79.4% were either current or ex-smokers, and 93.0% had stage IV (metastatic) NSCLC (Table 2). Over two thirds (69.5%) of patients were receiving first-line therapy for advanced disease with 30.5% receiving second or later lines of therapy. The majority of patients were receiving platinum-based doublet chemotherapy (44.3%), single-agent chemotherapy (22.2%), or an EGFR inhibitor (17.3%) regardless of line of therapy. Among 130 patients receiving a second- or later-line therapy, 8.5% were treated with immunotherapy.

Caregiver support

Over half (56.9%) of caregivers reported being the patients' only care provider, while a quarter (24.4%) reported that a formal (paid) caregiver also provided support (with or without any informal support). These results differed significantly across countries ($p < 0.0001$; Fig. 1a). The proportion of caregivers reporting they were the sole caregiver was lowest in France (43.1%) and highest in Italy (67.2%). Conversely, the proportion of caregivers who reported the patient also received support from a paid caregiver was highest in France (40.9%) and lowest in Italy (4.8%). The type of care provided ranged from emotional support and encouragement to help with eating and finances (Table 3).

Number of hours of support provided per week

In total, patients' caregivers reported a mean of 29.5 h of support per week was provided to patients ranging from 15.3 h per week

Table 1 Caregiver demographics

Characteristic	Overall ($N = 427$)	France ($n = 148$)	Germany ($n = 150$)	Italy ($n = 129$)
Age, mean (SD) years	53.5 (12.5)	56.4 (12.9)	50.2 (10.8)	53.8 (13.0)
Female, *n* (%)	307 (72.6)	118 (79.7)	90 (61.2)	99 (77.3)
Relationship to patient, *n* (%)				
Partner/spouse	234 (54.9)	100 (68.0)	62 (41.3)	72 (55.8)
Parent	3 (0.7)	2 (1.4)	0	1 (0.8)
Friend/neighbor	13 (3.1)	9 (6.1)	1 (0.7)	3 (2.3)
Child	136 (31.9)	21 (14.3)	76 (50.7)	39 (30.2)
Sibling	11 (2.6)	6 (4.1)	3 (2.0)	2 (1.6)
Other family members	12 (2.8)	6 (4.1)	0	6 (4.7)
Other	17 (4.0)	3 (2.0)	8 (5.3)	6 (4.7)
Employment status (%)				
Working full time	152 (36.2)	49 (33.3)	73 (49.7)	30 (23.8)
Working part time	37 (8.8)	9 (6.1)	18 (12.2)	10 (7.9)
Unemployed	35 (8.3)	18 (12.2)	8 (5.4)	9 (7.1)
Student	6 (1.4)	0	2 (1.4)	4 (3.2)
Homemaker	84 (20.0)	9 (6.1)	28 (19.0)	47 (37.3)
Retired	106 (25.2)	62 (42.2)	18 (12.2)	26 (20.6)

SD, standard deviation

Table 2 Patient demographics and clinical characteristics

Characteristic	Overall ($N = 427$)	France ($n = 148$)	Germany ($n = 150$)	Italy ($n = 129$)
Age, mean (SD) years*	66.2 (9.5)	65.2 (10.2)	66.1 (9.2)	67.4 (8.9)
Male, *n* (%)	293 (68.6)	111 (75.0)	89 (59.3)	93 (72.1)
Smoking status, *n* (%)				
Never-smoker	86 (20.6)	20 (13.6)	27 (18.2)	39 (31.7)
Current/ex-smoker	332 (79.4)	127 (86.4)	121 (81.8)	84 (68.3)
Histological type, *n* (%)				
Non-squamous	303 (71.0)	105 (70.9)	103 (68.7)	95 (73.6)
Squamous	124 (29.0)	43 (29.1)	47 (31.3)	34 (26.4)
Current NSCLC stage, *n* (%)				
Stage III	30 (7.0)	12 (8.1)	5 (3.3)	13 (10.1)
Stage IV	397 (93.0)	136 (91.9)	145 (96.7)	116 (89.9)
Brain metastases present, *n* (%)	61 (14.4)	31 (21.1)	21 (14.0)	9 (7.0)
Line of therapy, *n* (%)				
First	296 (69.5)	105 (70.9)	101 (67.8)	90 (69.8)
Second or later	130 (30.5)	43 (29.1)	48 (32.2)	39 (30.2)
First-line treatment regimens, *n* (%)	$n = 296$	$n = 105$	$n = 101$	$n = 90$
Single-agent chemotherapy	34 (11.5)	5 (4.8)	11 (10.9)	18 (20.0)
Single-agent chemotherapy + TA	6 (2.0)	4 (3.8)	0	2 (2.2)
Platinum-based doublet	179 (60.5)	77 (73.3)	56 (55.4)	46 (51.1)
Platinum-based doublet + TA	20 (6.8)	11 (10.5)	8 (7.9)	1 (1.1)
EGFR inhibitor	48 (16.2)	6 (5.7)	21 (20.8)	21 (23.3)
ALK inhibitor	5 (1.7)	0	4 (4.0)	1 (1.1)
Supportive care only	2 (0.7)	1 (1.0)	0	1 (1.1)
Other	2 (0.7)	1 (1.0)	1 (1.0)	0
Second- or later-line treatment regimens (%)	$n = 130$	$n = 43$	$n = 48$	$n = 39$
Single-agent chemotherapy	61 (46.9)	23 (53.5)	23 (47.9)	15 (38.5)
Single-agent chemotherapy + TA	6 (4.6)	2 (4.7)	4 (8.3)	0
Doublet chemotherapy	6 (4.6)	0	3 (6.3)	3 (7.7)
Platinum-based doublet	10 (7.7)	5 (11.6)	2 (4.2)	3 (7.7)
Platinum-based doublet + TA	3 (2.3)	3 (7.0)	0	0
EGFR inhibitor	26 (20.0)	8 (18.6)	5 (10.4)	13 (33.3)
ALK inhibitor	6 (4.6)	0	2 (4.2)	4 (10.3)
PDL1 agent	11 (8.5)	2 (4.7)	9 (18.8)	0
Supportive care only	1 (0.8)	0	0	1 (2.6)

TA, targeted agent; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *NSCLC*, non-small cell lung cancer; *PDL1*, programmed death ligand 1; *SD*, standard deviation

*1 patient reported to be 90+ years of age was assumed to be 90 years of age

in Germany to 45.6 h per week in Italy (across-country differences $p < 0.0001$; Fig. 1b). The mean percentage of the total care received by the patient that was provided by informal caregivers was 90.1% overall and ranged from 84.7% in France to 97.6% in Italy (across-country differences $p < 0.0001$).

Caregiver work productivity and activity impairment

At the time of the survey, 36.2% of caregivers were in full-time employment, 8.8% were in part-time employment, and 8.3% were unemployed (Table 1). Overall, 8.8% of patients reduced their working hours or changed their job as a result of their caregiver responsibilities, while 3 (0.8%) caregivers dropped out of work completely.

Among employed caregivers, the overall mean (SD) percentage work time missed in the last 7 days was 7.1% (11.4%), percentage impairment while working was 20.9% (24.7%), percentage overall work impairment was 25.7% (27.5%), and activity impairment was 32.8% (26.0%). The percentage impairment while working and activity

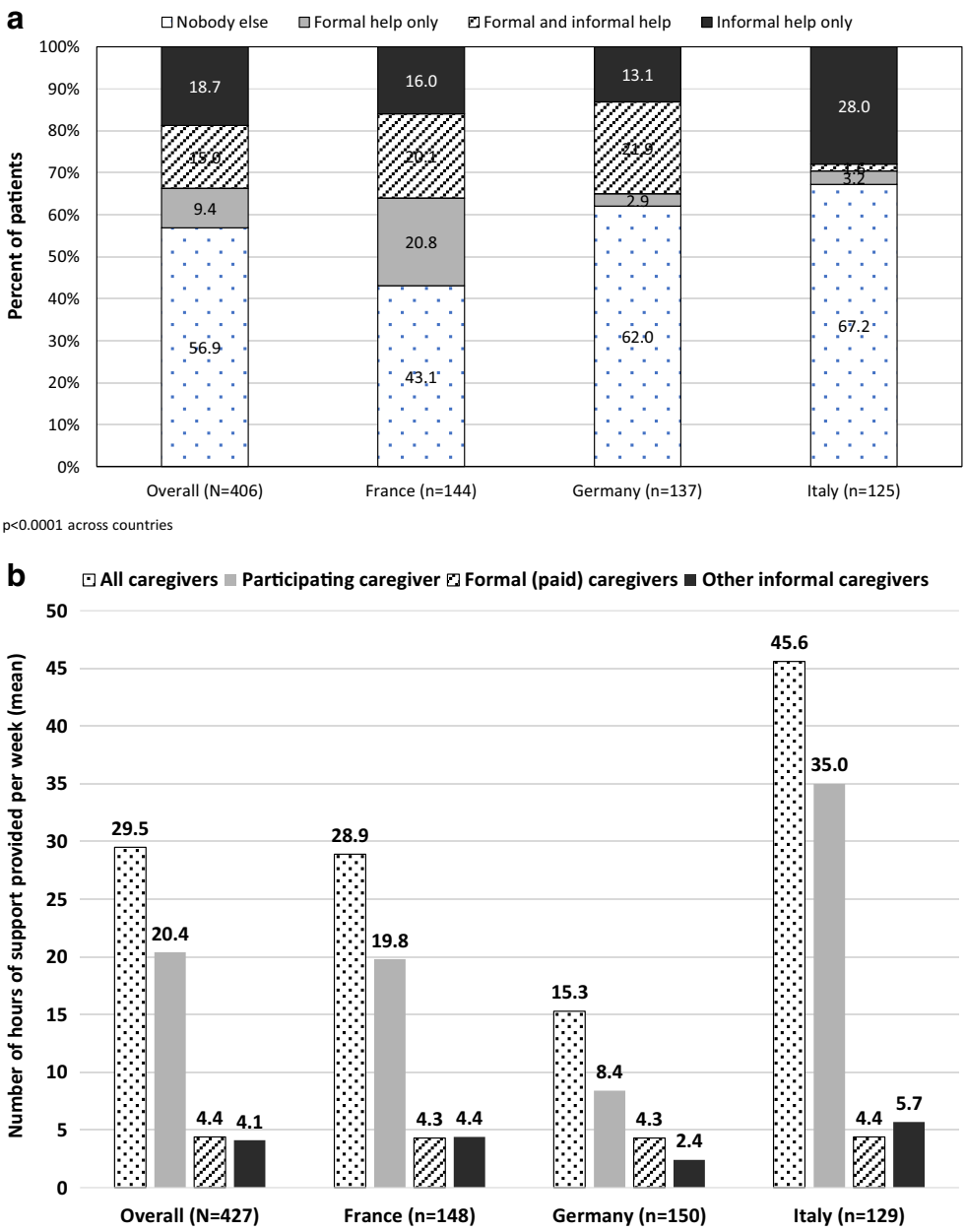

Fig. 1 Type of caregiver support provided (**a**) and number of hours of support provided per week (**b**) as reported by the accompanying caregiver

impairment differed significantly across countries (both $p < 0.05$ for across-country differences; Fig. 2a). Impairment while working was 16.4% in Germany, 25.8% in France, and 25.6% in Italy. Activity impairment was 23.2% in Germany, 38.6% in France, and 37.4% in Italy.

Although impairment was numerically higher among caregivers of patients receiving second or later lines of therapy for all WPAI domains, the differences were not statistically significant in the overall caregiver cohort (Fig. 2b). When stratified by line of therapy, impairment across all four domains of the WPAI were significantly higher among caregivers in France caring for patients receiving second or higher lines of therapy compared with those caring for patients receiving first-line therapy. The differences were not statistically significant among caregivers in Germany or in Italy.

Caregiver health state utility

Mean (SD) caregiver EQ-5D-3L scores were 0.89 (0.18) overall and 0.85 (0.23), 0.93 (0.15) and 0.91 (0.11) in France, Germany, and Italy, respectively ($p = 0.0002$). No statistically significant differences were noted for caregiver EQ-5D-3L scores in the overall cohort when stratified by patient line of therapy. There were statistically significant differences in EQ-5D-3L scores between caregivers of patients receiving first and later lines of therapy in France (0.87 vs. 0.78; $p = 0.0055$), but not in Germany or Italy.

Table 3 Caregiver support provided to patients

Support given, *n* (%)	Overall (*N* = 422)	France (*n* = 145)	Germany (*n* = 148)	Italy (*n* = 129)
None	22 (5.2)	3 (2.1)	17 (11.5)	2 (1.6)
Emotional support/encouragement	336 (79.6)	113 (77.9)	115 (77.7)	108 (83.7)
Drive them to work/hospital appointment	225 (53.3)	85 (58.6)	55 (37.2)	85 (65.9)
Help with preparing meals/cooking	195 (46.2)	92 (63.4)	48 (32.4)	55 (42.6)
Help with shopping	185 (43.8)	77 (53.1)	60 (40.5)	48 (37.2)
Help to remind patient to take medication	184 (43.6)	71 (49.0)	57 (38.5)	56 (43.4)
Help in giving treatment	152 (36.0)	56 (38.6)	44 (29.7)	52 (40.3)
Traveling out of home	148 (35.1)	81 (55.9)	12 (8.1)	55 (42.6)
Getting dressed/washed	142 (33.6)	46 (31.7)	42 (28.4)	54 (41.9)
Help plan and organize everyday activities	137 (32.5)	45 (31.0)	51 (34.5)	41 (31.8)
Help in advising on treatment options	125 (29.6)	57 (39.3)	41 (27.7)	27 (20.9)
Help getting in and out of bed	115 (27.3)	35 (24.1)	44 (29.7)	36 (27.9)
Communication with others	98 (23.2)	38 (26.2)	43 (29.1)	17 (13.2)
Help with going to the toilet	95 (22.5)	36 (24.8)	37 (25.0)	22 (17.1)
Eating	93 (22.0)	19 (13.1)	47 (31.8)	27 (20.9)
Finances	87 (20.6)	40 (27.6)	36 (24.3)	11 (8.5)
Help them research their condition	53 (12.6)	29 (20.0)	14 (9.5)	10 (7.8)
Using household appliances	46 (10.9)	22 (15.2)	9 (6.1)	15 (11.6)
Spend additional time looking after children	15 (3.6)	7 (4.8)	3 (2.0)	5 (3.9)
Other	3 (0.7)	2 (1.4)	1 (0.7)	0

With regard to self-reported health (EQ-VAS), the mean overall score was 80.3 (16.8) and 79.8 (19.2), 85.3 (13.8), and 74.4 (15.3) in France, Germany, and Italy, respectively ($p < 0.0001$). No statistically significant differences were noted for caregiver EQ VAS scores in the overall cohort when stratified by patient line of therapy. There were statistically significant differences in EQ VAS scores between caregivers of patients receiving first and later lines of therapy in France (82.7 vs. 72.9; $p = 0.0039$), but not in Germany or Italy.

Caregiver burden

Mean (SD) ZBI scores were 31.3 (15.0) overall and 31.5 (17.7), 29.8 (13.7), and 32.8 (12.9) in France, Germany, and Italy, respectively. Mean ZBI scores were numerically higher for caregivers of patients receiving second or later lines of therapy in the overall cohort although this difference did not reach statistical significance (Table 4). ZBI scores were statistically significantly higher for caregivers of patients receiving second or later lines of therapy in France (first line 29.3 vs. second or later line 36.7; $p = 0.0328$); this pattern was not observed for the caregiver cohort in Germany or in Italy.

The percentage of caregivers considered to be at risk for depression (ZBI total score ≥ 24 points) was statistically significantly higher among caregivers for patients receiving second or later lines of therapy in the overall cohort (first line 65.4% vs. second or later line 76.7%; $p = 0.0221$) (Table 3). The proportion of caregivers at risk for depression was numerically higher among those caring for patients receiving second or later lines of therapy in all three countries but did not reach statistical significance.

Discussion

The evaluation of the humanistic burden on caregivers of patients with advanced NSCLC presented here has shown that for most patients, care is provided informally by family members. The demographics of the caregiver population included in this study are in line with caregiver populations evaluated previously. Among a cohort of 64 caregivers providing care for patients with advanced cancer, caregivers were predominantly female (71.9%) with a somewhat higher mean age of 69.7 years than reported here (53.5 years) [28]. A meta-ethnographic evaluation of caregivers providing home palliative care for patients with mainly advanced cancer (90%) found that 765/814 (94%) caregivers were family members [29], consistent with the observation that in the cohort presented here, 86.9% of caregivers were either a partner/spouse or a child of the patient.

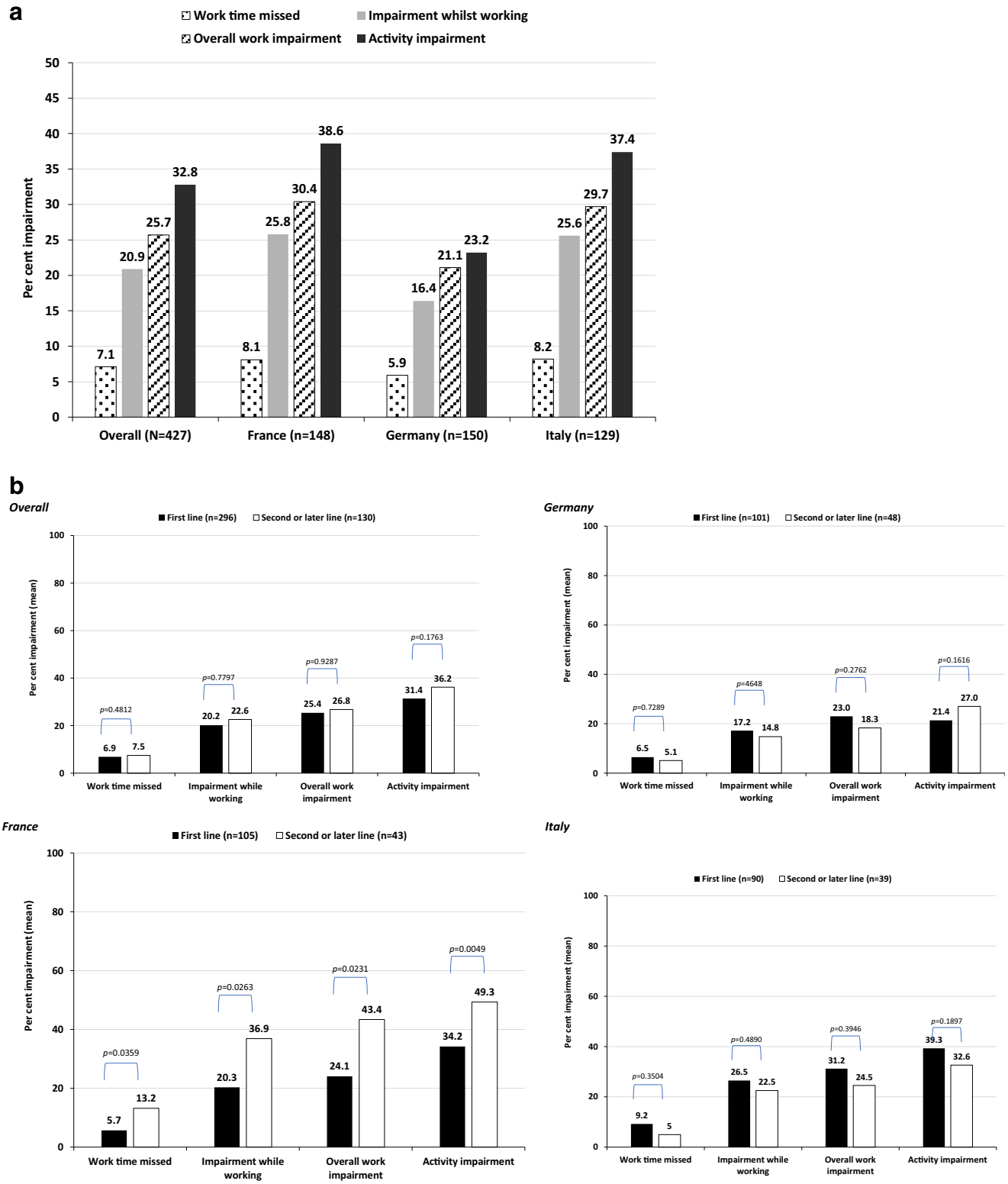

Fig. 2 Work Productivity and Activity Impairment (WPAI) domains overall (**a**) and stratified by line of therapy (**b**)

The average time spent providing care to patients by all caregivers was 29.5 h per week; a value that is close to that considered to be a full-time occupation in certain European countries. The Organisation for Economic Co-operation and Development (OECD) defines part-time employment as working < 30 h per week in the main job [30]. Despite the considerable number of care hours provided, caregivers reported only minimal time missed from formal work, ranging

Table 4 Caregiver ZBI scores overall and stratified by patient line of therapy for advanced disease for the total cohort and the French, Germany, and Italian cohorts

	Overall ($N = 416$)		France ($n = 142$)		Germany ($n = 149$)		Italy ($n = 125$)	
Mean total score (SD)	31.3 (15.0)		31.5 (17.7)		29.8 (13.7)		32.8 (12.9)	
Grouped, *n* (%)								
Little/no burden	103 (24.8)		40 (28.2)		39 (26.2)		24 (19.2)	
Mild/moderate burden	200 (48.1)		56 (39.4)		81 (54.4)		63 (50.4)	
Moderate/severe burden	101 (24.3)		41 (28.9)		24 (16.1)		36 (28.8)	
Severe burden	12 (2.9)		5 (3.5)		5 (3.4)		2 (1.6)	
At risk of depression, *n* (%)	287 (69.0)		95 (66.9)		101 (67.8)		91 (72.8)	
Line of therapy	First ($n = 286$)	Second or later ($n = 129$)	First ($n = 99$)	Second or later ($n = 43$)	First ($n = 100$)	Second or later ($n = 48$)	First ($n = 87$)	Second or later ($n = 38$)
Mean score (SD)	30.5 (15.0)	33.0 (14.8)	29.3 (17.3)	36.7* (17.6)	29.6 (13.2)	29.9 (14.8)	32.7 (14.0)	32.9 (10.1)
Grouped, *n* (%)								
Little/no burden	76 (26.6)	27 (20.9)	31 (31.3)	9 (20.9)	27 (27.0)	12 (25.0)	18 (20.7)	6 (15.8)
Mild/moderate burden	134 (46.9)	65 (50.4)	40 (40.4)	16 (37.2)	54 (54.0)	26 (54.2)	40 (46.0)	23 (60.5)
Moderate/severe burden	68 (23.8)	33 (25.6)	25 (25.3)	16 (37.2)	16 (16.0)	8 (16.7)	27 (31.0)	9 (23.7)
Severe burden	8 (2.8)	4 (3.1)	3 (3.0)	2 (4.7)	3 (3.0)	2 (4.2)	2 (2.3)	0 (0)
At risk of depression, *n* (%)	187 (65.4)	99 (76.7)*	61 (61.6)	34 (79.1)	64 (64.0)	36 (75.0)	62 (71.3)	29 (76.3)

SD, standard deviation

*$p < 0.05$ for caregivers of patients on first-line therapy versus second or later lines of therapy for advanced NSCLC

from 5.9% in Germany to 8.1% in France and 8.2% in Italy. However, among employed caregivers, overall work impairment was considerable and ranged from 21.1% in Germany to 30.4% in France and 29.7% in Italy. These observations suggest that while caregivers may not miss many formal work hours, their performance at work may be considerably impaired because of the number of hours they are required to provide care for the patient with advanced NSCLC.

As noted, the caregiving cohort included in the current analysis was predominantly family members. Recent studies have highlighted the satisfaction caregivers can achieve from their caregiving activities [14, 31, 32]. Nonetheless, caregiving can have negative implications for the caregiver's own health and emotional well-being [13–15]. The results of the caregiver health utility analysis using the EQ-5D-3L revealed only mild health state impairment [33]. However, given that this instrument includes dimensions that may be related more to a disease state than a humanistic burden (pain/discomfort, mobility, and self-care), this tool may not have been sufficiently incisive to detect caregiver-specific health state impairments. Despite this, significant differences in EQ-5D-3L scores were observed between caregivers of patients receiving first and later lines of therapy in France (0.87 vs. 0.78; $p = 0.0055$). Moreover, caregivers of patients in France receiving later lines of therapy rated their own health status as significantly worse than did those caring for patients receiving first-line therapy (82.7 vs. 72.9; $p = 0.0039$). The caregiver burden measured by the mean ZBI reported here was greater than that reported previously for caregivers of patients with advanced cancer (mean ZBI 18.5; [28]), irritable bowel disease (mean ZBI 22.1; [34]), Parkinson's disease (mean ZBI 25.8; [35]), or chronic liver disease (mean ZBI 22.4; [36]) and was similar to that seen for caregivers of patients with Alzheimer's disease (mean ZBI spouse 28.1, mean ZBI adult-child 31.8; [37]). As observed for health states measured using the EQ-5D-3L, ZBI scores differed by line of therapy in France (first line 29.3 vs. second or later line 36.7; $p = 0.0328$).

Together, these observations highlight a range of burdens experienced by caregivers of patients with advanced NSCLC including potential reductions in health state perception, increased risk for depressive illness, decreased performance at work, and decreased overall activities related to caregiving. Although informal caregivers play a critical role in supporting patients with advanced NSCLC, a role that would otherwise need to be provided by the healthcare or social care system, this is not without a cost to the individual and potentially to the wider society. The observed work impairment data suggest an economic cost on work productivity, and the increased risk for depressive illness suggests a potential cost to the healthcare system.

Overall, caregivers providing care for patients receiving second or later lines of therapy were at statistically significantly greater risk for depression than were those caring for patients receiving first-line therapy. A previous study showed that caregiver burden was affected more by patient QoL than by lung cancer stage [5]; this observation highlights the potential impact on the mental health of caregivers as the patients' disease progresses. The descriptive nature of the

current study did not enable the relative contribution of increasing symptomatology with disease progression and the burden of treatments to be evaluated. Country-level analyses revealed notable differences in terms of caregiver burden and work impairment among caregivers in France compared with those in Germany and Italy. In France, caregivers were somewhat older and more likely to be female and a spouse to a patient with NSCLC. They also reported a statistically significantly greater burden (ZBI score) when caring for patients receiving second or later lines of therapy compared with patients receiving first-line therapy, a difference that was not observed for caregivers in Germany or Italy. In addition, they reported significantly greater work impairment when caring for patients receiving second or later lines of therapy compared with patients receiving first-line therapy, again, a difference that was not observed for caregivers in Germany or Italy. The reasons for the markedly increased burden for caregivers in France of patients receiving later lines of therapy are not immediately apparent. More patients in France were receiving only formal caregiver support and French caregivers provided markedly fewer hours of care each week than did those in Italy (19.8 vs. 35.0 h).

An analysis of data from the European Social Survey Round 7, which included 32,894 individuals in 19 European countries, showed that the prevalence of informal caregiving varied considerably among European countries [22]. For the purposes of the current research, France represented a country of relatively high levels of informal caregiving and Germany of moderate levels—close to the mean proportion across the 19 countries included in the analysis. This previous research also found that although Southern European countries trended towards lower levels of informal caregiving, the intensity of the caregiving (the number of hours each week) was higher than for Northern European countries [22]. Thus Italy, although not included in the previous research [22], could be expected to represent a country of relatively low level of informal caregiving but with high intensity informal caregiving. Consistent with these previous observations, the number of hours per week of informal caregiving and the proportion of total care provided by informal caregivers were highest in Italy. Moreover, the ZBI scores and proportion of caregivers at risk for depression were highest for caregivers in Italy, although the differences were small. Caregivers are predominantly female across European countries [38]. The current study revealed considerable differences among countries in this respect with the proportion of female caregivers being considerably lower in Germany (61.2%) than in either France (79.7%) or Italy (77.3%). Cultural differences in terms of familial structure may contribute to this apparent gender bias among countries although there is a paucity of systematic data on this issue. Policy differences in terms of formal care provision may partially explain these differences. A study in 2011 suggested differences in the burden of informal care between Belgium and the UK may be a consequence of better targeting of long-term home care policies to more severely dependent patients in the UK than in Belgium [39]. The analysis of the European Social Survey Round 7 described above highlighted considerable variation in terms of the generosity of formal long-term care provision among European countries, with above average provision in France and considerably below average provision in the UK [22]. These observations suggest that organizational features of healthcare systems to provide home care support services may have an impact on informal caregiver burden [22]. Further research to identify factors influencing caregiver burden between healthcare systems is warranted and may reveal best practice learnings to inform future service improvements.

Although beyond the scope of the current analysis, recent studies have explored the impact of caregiver burden and mental health on caregiving capabilities and the subsequent impact on patients [40, 41]. In a study of 88 dyads of patients with glioblastoma multiforme and their family caregivers, caregiver mastery (a measure of how confident the caregiver feels in the caregiving capabilities) was shown to predict patient survival. Greater caregiver demand burden was shown to be associated with deceased patient survival among 123 caregiver-patient dyads for patients with advanced cancer [42]. In a separate study among 910 spouse-cancer survivor dyads, depressed mood and HRQoL of spouses increased the risk of depressed mood in cancer survivors [43]. In fact, other recent analyses suggest that close interrelationships exist between caregivers and patients with regard to perceived burden, QoL, and mental health status [44]. Such observations suggest that caregivers and patients should be viewed as an interdependent unit when considering supportive care interventions and that such interventions have the potential to impact patient outcomes [44].

The strengths of the current analysis are the cross-sectional, multi-country, multi-dimensional approach, which has permitted alignment of patient characteristics with caregiver burden, thus demonstrating an increased burden in terms of health state (EQ-5D-3L) and feelings of burden experienced by caregivers and their risk of depressive illness (ZBI). The selection of three EU countries with very different attitudes/approaches to caregiving permitted consideration of country-specific differences. Indeed, differences were noted regarding hours of care provided, impact on formal work attendance and performance, and reported caregiver burden. These observations highlight the need for future studies to explore the country-specific context of caregiving (such as availability of formal care, availability and affordability of dedicated palliative care teams) and how this might frame the burden placed on caregivers.

Several limitations should be considered when considering the results presented here. The population was sampled from patients presenting for physician care and their accompanying

caregivers. As such, the patient and caregiver population may not fully represent the wider non-presenting population of patients with NSCLC and their caregivers, or caregivers not accompanying the patient to the clinic visit. The study was designed as a cross-sectional investigation and therefore relied both on self-reporting and recall of the participants. Our data do not therefore provide information on the evolution of caregiver burden over time. Data are presented descriptively and therefore do not consider any potential confounding factors that might influence perceived burden or QoL as reported by caregivers. Moreover, no causal inferences can be made from the data presented here although potential associations for further investigation have emerged. At the time of the study, immunotherapy for NSCLC was not widely available. This is reflected in the treatment profile of the patient cohort who received principally platinum-based chemotherapy.

Conclusions

In conclusion, our study has demonstrated that informal caregivers provided the majority of support for patients with advanced NSCLC and that their caregiving activities imposed a significant humanistic burden. While caregivers play a vital role in unburdening institutions and releasing resources (reducing the burden on the healthcare system), consideration of the humanistic burden on the caregiver in any healthcare assessment is essential to evaluate the holistic burden of caring for patients with advanced NSCLC.

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Compliance with ethical standards

The study protocol was approved by a central Institutional Review Board (Freiburg Ethics Commission International—Ref 015/1196).

Conflict of interest Robert Wood and Gavin Taylor-Stokes are employees of Adelphi Real World, a consultancy to the health insurance and life science industries. Michael Lees was an employee of Bristol Myers Squibb, the sponsor of this research and a global biopharmaceutical company that researches and develops medicines for NSCLC, at the time the study was conducted.

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