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Analysing the influencing factors on caregivers' burden among ALS patients in China based on data mining

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32	19						
33	20	Abstract:					
34 25	21	Objective: There is significant burden on caregivers of patients with amyotrophic lateral sclerosis					
35 36	22	(ALS). However, only a few studies have focused on caregivers, and traditional research methods					
37	23	have obvious shortcomings in dealing with multiple influencing factors. This study was designed to					
38	24 25	explore influencing factors on caregiver burden among ALS patients and their caregivers from a new					
39	$\frac{23}{26}$	Perspective. Mathade: Fifty seven nationts with ALS and their caregivers were investigated to analyse the factors					
40	$\frac{20}{27}$	influencing caregiver burden through data mining. Statistical analysis was performed using SPSS					
41 42	28	24.0, and LASSO regression model was established by python 3.8.1 to minimize the effect of					
42 43	29	multicollinearity.					
44	30	Results: According to LASSO model, we found ten variables had weights. Among them, MITOS					
45	31	stage(0-1) had the highest weight (-12.235), followed by younger age group(-3.198) , lower-educated					
46	32	group (2.136), fatigue(1.687), and social support(-0.45). Variables including sleep quality, anxiety,					
47	33	depression, and sex(man) had moderate weights in this model. Economic status(common), economic					
48	34	status(better), household(city), household(village), educational level(high), sex(female), age(older),					
49 50	35	MITOS stage(2-4), had a weight of zero.					
50 51	36	Conclusions : Our study demonstrates that caregiver burden is positively correlated with the degree					
52	37	of fatigue and negatively correlated with social support. Low educational status could increase					
53	38	caregiver burden. Caregivers of ALS patients may suffer less from caregiver burden when the					
54	39	patients was younger and less severe. Hopefully, more attention should be paid to caregivers of ALS					
55	40	and effective interventions can be developed to relieve this burden.					
56	41	Keywords: ALS: caregiver burden: LASSO: social support: MITOS: fatigue					
57 58	49	Keywords, 1120, caregiver burden, 21000, social support, wir100, langue					
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Strengths and limitations of this study ∻ ∻ ∻ ∻ ∻ 1. Introduction burden.

- This was the first time we study influencing factors on caregiver burden among ALS patients and their caregivers through data-mining based on LASSO regression.
- The research method solves the problem of small sample size and multicollinearity among independent variables.
- Different kinds of continuous variables and categorical variables were involved in the study.
- This was a study conducted in south-eastern China, which may only represent a part of the Chinese population.
 - Our analysis did not include intervention effects with quantified coping strategies in a prospective study.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with progressive muscle weakness, dysarthria, dyspnoea, dysphagia, and other associated symptoms which prevent patients from taking care of themselves. Patients become increasingly dependent on their partners, family members, and other relatives for increasing support and assistance. For one thing, the high cost of medical care, drugs, and other supportive services exert huge pressure on families with ALS patients. Moreover, the influence on family in caregiving of patients with ALS is great[1; 2]. The role of caregivers is critical because their health and well-being are not only important for patients[3] [4]. Moreover, as the disease progresses, patients will suffer from worsening health and diminishing quality of life. Thus, as the disease progresses, the concomitant psychological distress and mental stress of informal caregivers of ALS increase significantly[5]. This phenomenon has also been observed in other neurodegenerative diseases[6] [7]. Kim et al. found a negative correlation between the time spent in caregiving and quality of life of caregivers[8]. In Burke's study, patients' cognitive and behavioural status is of great importance as mediators of caregiver burden[9]. While these studies have demonstrated factors that were associated with an increasing burden for caregivers, we only found a few studies that have focussed on influencing factors of caregivers, such as physical health, psychological symptoms, social background, social support, and the patients' condition, and most of them were designed as cross-sectional studies or case-control studies[10-15]. Also, knowledge about the action of interventions in relieving caregiver burden is still limited.

This study aimed to determine the effect of factors that influence caregivers' burden and physical and mental health through data mining based on LASSO regression model. Hopefully, effective interventions can be developed to improve the health status of caregivers and help relieve caregiver

2. Materials and Methods

2.1 Resource of data and participants

Caregivers of patients registered at First affiliated hospital of Sun yat-sen University(FAH-SYSU) from August 2015 to February 2017 and with a patient diagnosis of ALS according to the revised El Escorial criteria were recruited in the study. As this retrospective study was an analysis of existing data, which did not involve patients' or caregivers' diagnosis and treatment, no ethics approval was required from the Ethics Committee of FAH-SYSU. Even though, participants enrolled have been fully informed and consent was obtained. Healthy caregivers with at least 3 months' caregiving experience were included in the study, and caregivers were restricted to relatives such as spouses, parents, children, and siblings of the patients. Informal, casual, or multiple caregivers and those with confirmed physical and mental problems were excluded. Patients who had rapid deterioration since diagnosis or with bulbar/spinal/respiratory breakdown were excluded from the sample.

This study primarily assessed the influencing factor of caregiver burden including age, gender, education level, economic status, anxiety, depression, social support, fatigue, sleep quality, as well as

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the duration and stage of disease(MITOS stage). The quantitative questionnaires of standardised design assessed caregiver burden on different dimensions. Standardised scales were used for the caregivers, listed in the following section. In total, 60 caregivers of ALS patients were selected for the survey through internationally accepted questionnaires. Among all the 60 questionnaires sent out to the caregivers, 57 valid responses were received, with a valid rate of 95%. 2.1.1 Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. 2.2 Assessment measures and data collection 2.2.1 Patients' status Disease duration was measured by months. Disease severity was mainly measured by the clinical staging system of Milano-Torinos (MITOS)^[16]. According to this staging system, patients with ALS are categorised as follows: Stage 0, functional involvement but no loss of independence in any domain; Stages 1-4, which refer to the number of domains in which independence was lost, for example, movement, swallowing, communicating, and/or breathing; and Stage 5, death. 2.2.2 Caregiver burden Zarit Caregiver Burden Interview (ZBI) was used to evaluate caregiver burden. ZBI consists of a self-administered 22-item questionnaire, including caregivers' psychological health, finances, emotional wellbeing, social and family life, and degree of control over their life. Total scores range between 0 and 88. 2.2.3 Social support The Social Support Rating Scale (SSRS) is a brief questionnaire designed by Xiao Shuiyuan in 1986-1993, which mainly reflects social support and satisfaction with social support from the respondents. 2.2.4 Physical and mental health of caregivers The sleep quality of caregivers was assessed using the Pittsburgh Sleep Quality Index (PSQI). Fatigue scale-14 (FS-14) was used to measure the severity of physical and mental fatigue and its effect on a person's activities and lifestyle. Anxiety and depression status were evaluated using the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale-17 (HAMD-17). 2.3 Statistics 2.3.1 General characteristics Statistical analysis was performed using SPSS 24.0 and Python 3.8.1. Descriptive statistics were used for categorical variables. Means with a standard deviation(SD) and interquartile range(IQR) were used for continuous variables. Bivariate correlations between continuous variables were performed by Pearson correlation analysis. Correlations between caregiver burden and categorical variables were analysed by visualization analysis. All tests were performed with an alpha value of 0.05. 2.3.2 Least Absolute Shrinkage and Selection Operator (LASSO) regression Least Absolute Shrinkage and Selection Operator (LASSO) regression was used to establish a model to predict the relationship between caregiver burden and variables with high multicollinearity. LASSO was a regression technique for variable selection and regularization to enhance the prediction accuracy and interpretability of the statistical model that it produces. It was a constrained version of ordinary least-squares (OLS) regression and typically used for regression

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of a single response variable y on a predictor matrix X, which was widely used in dealing with data situations of low sample size and high dimension, especially when there were both continuous variables and categorical variables in the regression[17].	
Compared with other linear regression, lasso was more applicable to analyse complex multicollinear data by adding a penalty equal to the absolute value of the importance of coefficients and minimizing insignificant coefficients to 0, thus the high weight variables will be selected. The absolute size of the regression coefficients β was constrained. The higher the penalty, the more regression coefficients were shrunk toward zero. The regularized regression is quite sensitive to the selection of the penalty coefficients. [18-20]	
To appropriately tune the best parameter, the approach was to estimate the performance with different values using cross-validation[21]. Compared with other methods, LASSO was fast and accurate with the advantage of avoiding overfitting automatically.	Protected b
2.3.3 Prediction Performance Evaluation The mean square error (MSE) between the predicted value and the actual value was used to evaluate prediction performance. The coefficient of determination R ² was used to reflect the regression fitting effect of the prediction model. The coefficient R ² is defined as (1 - u/v), where u is the regression sum of squares ((y_true - y_pred) ** 2).sum() and v is the residual sum of squares ((y_true - y_true.mean()) ** 2).sum(). Best possible score is 1.0, and lower values are worse. Lasso best(alpha) parameter was obtained by cross-validation (CV). The algorithms were implemented using the Lasso CV package of sklearn in Python 3.8.1.	y copyright, including for
2.4 Data processing and dummy variables In order to incorporate categorical variables and continuous variables into the LASSO regression model, each variable was processed according to the research purpose. Since continuous variable "age" followed a skewed distribution by calculation of skewness and kurtosis, age was categorized into two groups as categorical variables. Categorical variables were reclassified and served as dummy variables to make the regression result with a positively explanative sense. Dummy coding method represents group membership with dummy variables that take on values 0 and 1, meaning that membership in a particular group is coded one whereas non- membership in the group is coded zero. When dummy coding is used in the regression analysis, the overall results indicate whether there is a relationship between the dummy variables and the dependent variables[22]. The values of the intercept and the regression coefficients of the resulted regression model can be obtained using least squares estimation procedures. The coefficient of multiple determination, R ² , for the regression model with dummy variables can be interpreted in terms of the proportion of variance in the dependent variable that is accounted for by the categorical independent variable[23]. The regression model from the dummy coding can be written as: $Y_{ij} = B_0 + \sum_{i=1}^{k-1} B_j D_{ij} + \varepsilon_{ij}.$	Enseignement Superieur (ABES) . uses related to text and data mining, Al training, and s
Where: $Y_{ij} = 2_0 + 2_{j-1} + 2_j + 2_{ij} + 2_{ij}$. W_{ij} : The score on the dependent variable for subject i in group j. B_0 : The intercept that represents the mean of the group coded 0 on all the dummy variables. k: The number of categories of the independent variable. B_j : The regression coefficient associated with the jth group, and it represents the difference between the mean of the group coded 1 on the corresponding dummy variable and the mean of the group coded 0 on all the dummy variables. D_{ij} : The numerical value assigned to subject i in the jth group. ε_{ij} : The error associated with the ith subject in the jth group. To be specific, categorical variables were recoded with dummy variables, including 2 dummy variables suggesting age, 2 dummy variables suggesting MITOS stage, 2 dummy variables suggesting economic status. 2 dummy variables suggesting household, and 2 dummy variables	similar technologies.

suggesting economic status, 2 dummy variables suggesting househo suggesting educational level(Table 1). The principle of the setting of dummy variables was to

equalize numbers between groups and accord with the meaning of each variable value. For example, educational level (low) represented the sum of educational status including illiterate, primary school, middle school, and high school, while educational level(high) represented the sum of educational status including junior college, undergraduate, and master. Overall, 6 continuous variables, together with 12 dummy variables of 6 categorical variables were introduced into the model.

Table 1 The variable weight of the LASSO regression and description of dummy variables

<i>Continuous variables</i> Duration PSQI	0.077	
Continuous variables Duration PSQI	0.077	
Duration PSQI	0.077	
PSQI	0.077	
	0.078	
FS-14	1.687	
Anxiety	0.043	
Depression	0.004	
Social support	-0.455	
Categorical variables		
Sex(male)	-0.171	
Sex(female)	0	
Age(younger)	-3.198	<35
Age(older)	0	≥35
MITOS(stage 0-1)	-12.235	MITOS stage 0,1
MITOS(stage 2-4)	0	MITOS stage 2,3,4
Economic status(common)	0	poor, average
Economic status(better)	0	good, excellent
Household(village)	0	suburban, rural
Household(city)	0	city
Educational level(low)	2.136	illiterate
		primary school
		middle school
		high school
		technical secondary scho
Educational level(high)	0	junior college
		undergraduate
		master

3.1 Descriptive analysis of characteristics of caregivers and ALS patients

The majority of this cohort was two-thirds female caregivers (38, 66.7 %), and the other one-third were male caregivers (19, 33.3%). The mean age of all the caregivers was 45.32±13.74 years(IQR: 33.5-56.5), ranging from 22-72 years. The average disease course was 28.98±15.36 months(interquartile range, IQR: 18-36), with the longest being 60 months and the shortest being 6 months. The average score of caregiver burden scale was 39.28±17.11(IOR:25-55). The average scores of PSQI and FS-14 were 7.89±4.57(IQR:4-10), 6.58±3.60(IQR:4-9), respectively. The average HAMA scores of patients were 10.70±6.62(IQR:5-15). The average HAMD scores of patients were 10.16±8.78(IQR:4-14.5). The mean score of the Social Support Rating Scale was 40.18±7.47(IQR:33.5-46). Forty caregivers were considered "anxious" to different degrees, and the number of possible, definite, obvious, and severe anxiety status caregivers were 20,15,4,1, respectively. Similarly, 27 caregivers were considered "depressed", and the number of possible, moderate, and severe depression status caregivers were 16,10,1, respectively. For categorical variables, the number of

patients with MITOS from zero to stage 4 was 10,16,20,4,7, respectively. Most of the caregivers were
junior high school graduates (17, 29.8%). Overall, 34 participants (59.6%) had an education level of
at least high school, of which two held a master's degree. Urban dwellers constituted a proportion
of 56.1% of all the caregivers, while the rest of the individuals were from suburban or rural areas.
Economic status varied from general to good condition among the participants (Table 2).

	0 1	0					
		Ν	N%			Ν	N%
gender				MITOS			
	male	19	33.3		stage 0	10	17.5
	female	38	66.7		stage 1	16	28.1
education					stage 2	20	35.1
	illiterate	1	1.8		stage 3	4	7.0
	primary school	4	7.0		stage 4	7	12.3
	middle school	17	29.8				
	technical	1	1.8				
	secondary			economic			
	school			state			
	high school	12	21.1		poor	5	8.8
	junior college	10	17.5		average	21	36.8
	undergraduate	10	17.5		good	9	15.8
	master	2	3.5		excellent	22	38.6
househol	Rural	18	31.6	Age			
d register							
	suburban	7	12.3		<35	15	26.3
	city	32	56.1		≥35	42	73.7
				total		57	100%

Table 2 Demographic features of caregivers

224 3.2 Analysis of correlations between continuous variables

Correlations between continuous variables were demonstrated with Heatmap Chart shown in Figure 1. According to Spearman correlation analysis, positive correlations were seen between caregiver burden and independent variables including duration of disease, PSQI scores, degree of fatigue, anxiety, and depression(r=0.52, 0.54, 0.76, 0.71, 0.62, p<0.05), while a negative correlation was noted between caregiver burden and social support(r= -0.41, p<0.05). Interestingly, a slight negative correlation was noticed between social support and PSQI scores, degree of fatigue, and depression(r= -0.33, -0.29, -0.37, p<0.05), indicating that social support could be a protective factor. Strong pairwise positive correlations were seen among PSQI scores, degree of fatigue, anxiety, and depression(p<0.05).

233 3.3 Analysis of correlations between caregiver burden and categorical variables

Correlations between caregiver burden and categorical variables were shown as visualizations (Figure 2). We used layered data processing to rearrange categorical variables and convert them into dummy variables. The principle of the setting of dummy variables was to equalize numbers between groups. The descriptions of each dummy variable were shown in Table 1. Figure 2 (1) showed that there was a difference in caregiver burden between younger and older patients. Also, an obvious disparity in caregiver burden was seen between group MITOS stage(0-1) and group MITOS stage(2-4), suggesting that patients with ALS with severer symptoms created higher caregiver burden(Figure 2 (5)).

- 242 3.4 Model construction and evaluation by Lasso regression
 - 243 3.4.1 Variable Selection

The values of each categorical attribute were converted into dummy variables to build a

regression model. With caregiver burden as the dependent variable and duration, PSQI, FS-14, anxiety, depression, social support, sex(male), sex(female), age(younger), age(older), MITOS stage (0-1), MITOS stage(2-4), economic status(common), economic status(better), household(village), household(city), educational level(low), educational level(high) as independent variables, a regression model with multiple dummy variables was constructed shown in Table 1. In the LASSO model, we found ten variables had weights. Among them, MITOS stage(0-1) had the highest weight (-12.235), followed by younger age group(-3.198), lower-educated group (2.136), fatigue(1.687), and social support(-0.45). Variables including sleep quality, anxiety, depression, and sex(man) had moderate weights in this model. Economic status(common), economic status(better) ,household(city), household(village), educational level(high), sex(female), age(older), MITOS Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies. In this research, the mean squared error (MSE) was selected as the evaluation index, and the best Alpha value was obtained through cross-validation. The relationship between the model MSE and Alpha is shown in Figure 3. When the best penalty factor 'Alpha'= 0.3, the MSE is the smallest, and the LASSO regression model has the highest accuracy. To evaluate prediction performance and fitting effect, the R² and the MSE of the LASSO regression model were provided. The Lasso $score(R^2)$ and the lasso MSE were 0.831 and 48.496, respectively. 3.5 Liner regression analysis between MITOS stage(0-1), FS-14, and caregiver burden In the previous section, we learned from the LASSO regression model that MITOS stage(0-1) had the highest weight among categorical variables, while FS-14 had the highest weight among continuous variables. Moreover, the coefficient of MITOS stage(0-1) was significantly higher than other influential dummy variables, and the coefficient of FS-14 was even hundreds of times higher than other continuous variables. Therefore, to furtherly validated the action of the most influential factors in the model, a linear regression model was constructed with caregiver burden as the

dependent variable, and FS-14, MITOS stage (0-1) as independent variables. 3.5.2 Performance evaluation As was shown in Figure 4, caregiver burden was positively correlated with FS-14 whenever dummy variable MITOS stage(0-1) was kept in the model or not. On the other hand, when FS-14 remained constant, caregiver burden was significantly higher when dummy variable MITOS stage(0-1) was absent. The distance between the red line and the green line demonstrated the influence of MITOS stage(0-1) on caregiver burden in the model. The intercepts of the linear regression model was 32.125. The Lasso score(R^2) and the lasso MSE were 0.783 and 62.46, respectively. The results were consistent with LASSO regression, suggesting that MITOS stage(0-1)

had a strong effect on caregiver burden.

stage(2-4), had a weight of zero (Table 1).

3.4.2 Performance evaluation

3.5.1 Variable selection

4. Discussion

Based on the LASSO model, 10 variables had weights, whereas 5 variables had a greater influence on the model. MITOS stage(0-1) had the highest weight (-12.235), followed by younger age group(-3.198), lower-educated group (2.136), fatigue(1.687), and social support(-0.45). According to the results mentioned above, MITOS stage of patients with ALS was the most important factor influencing caregiver burden, and caregiver burden was significantly lower in patients of ALS with a milder type (MITO stage 0-1). Interestingly, when another variable duration of disease was brought into the regression model, it didn't show any effect on the model, indicating that compared to duration, the severity of patients with ALS had a greater influence on caregiver burden. Sarah K. Bublitz found that thick mucus was a highly distressing symptom for both

292 patients and caregivers, which caused a higher degree of bulbar impairment and had a strong
 293 impact on their quality of life[24].

We draw a conclusion from our study that caregiver burden was positively correlated with the degree of fatigue, while the correlation between caregiver burden and psychological factors such as anxiety and depression was relatively weak. The research of Brizzi K T et.al also showed that the pressure of caregiving in ALS originated from physical symptoms consisting of fatigue, pain, weakness, shortness of breath, difficulty sleeping, and speech problems, as well as depression and other mood changes. It was worth noting that fatigue and weakness were the most common symptoms and happened in over 75% of respondents [25], which was in accordance with our study. In our LASSO model, fatigue had higher weights than anxiety, depression, and sleep quality. Physical exhaustion was also a typical feature of caregiver burden of other progressive diseases, such as Alzheimer's disease, Parkinson's disease, and cancer[26-29]. Not surprisingly, the feelings of fatigue probably came from long-distance travel to the hospital for treatment, strenuous work in caregiving, and loss of rest time. This could well explain our result that younger caregivers suffered less from caregiver burden because they were healthier and more energetic, although they needed to consider time-consuming costs and balance between work and caring. For those younger caregivers, their caring patients were also younger as most of the caregivers were their spouses. This could be another reason that younger caregivers experienced less caregiver burden.

In this study, we found that caregiver burden was negatively correlated with social support, which was consistent with a study in Korea [30]. According to the epidemiology of ALS in China, we have a potentially lower incidence and prevalence of ALS than in foreign countries [31]. It is still a rare disease so doctors with less experience may fail to make a correct diagnosis in time and provide appropriate treatment. Even if the diagnosis is clear, effective treatment is not always available to every family due to the high cost of treating the illness. Fortunately, ALS is gradually being covered by health insurance in many provinces of China. The guarantee of a new policy is of great importance in helping relieve the economic burden on caregivers. In addition to economic support, more attention was paid to this group because of increasing caring activities, media reports, and social propaganda such as the "Ice Bucket Challenge" all over the country[32]. Multiple-center clinical studies of potential drugs based on animal experiments have also been conducted by a great number of Chinese research teams [33; 34], bringing hope and light to patients and caregivers of ALS.

On the other hand, according to our study, social support only had a modest action on caregiver burden. This phenomenon might be caused by insufficient and unbalanced social support in China. Therefore, we speculated that greater social support would bring about less caregiver burden. In some well-developed regions such as Hong Kong, the promotion of multidisciplinary teams (MDT) provides effective support for the disease, which encourages patients and families of ALS in a highly positive manner[35]. Family care is the main strategy for Chinese caregivers to look after ALS patients, and older women and spouses still play an important role in providing family care, while in some other countries, hospital care, nursing home care, and community care were made full use of to help alleviate the families' burden [36; 37]. The lack of professional caring experience, staff, and facilities could affect the efficiency of caring and thus lead to an increasing caregiver burden. Although China has developed rapidly in recent years, there have been obvious differences in medical development and medical investments between eastern and western areas. Little research on ALS has been conducted in western areas, where economic conditions are relatively poor and social support is inadequate. In contrast, modern countries, such as Japan and other European countries can offer stronger social aid and help systems to ALS families through long-term care insurance, home visit rehabilitation, and peer group rehabilitation, suggesting that more social support could be provided to Chinese ALS caregivers to relieve their burden [13; 37-40]. In addition, medical expenses and end-of-life care were guaranteed in well-developed countries like Japan. Obviously, there is an urgent need for more economical, practical, physical, emotional, and spiritual support for caregivers of ALS.

342It was surprising to find in our study that educational level influenced caregiver burden. In this60343study, caregivers of ALS patients were mainly their spouses who were of the same age (50-70y) and344had similar educational levels (middle school) to the patients. A possible explanation is that

understanding abilities varied among different caregivers and could be a limitation in low-educated groups. Under the current situation in China, patients were not able to address all their questions in a short period because of the large hospital outpatient quotas. For those caregivers who had a lower educational level, they might feel difficult to quickly understand the key points in caring and follow doctors' suggestions. In addition, they possibly lacked the abilities to search for information and teach themselves to improve the efficiency of home nursing work.

We investigated the correlations between caregiver burden and caregivers' mental states, including anxiety, depression, sleep quality index, and fatigue. Although we observed a slight correlation between anxiety, depression, and caregiver burden, they didn't show high weights in the LASSO regression model as we expected. In contrast with other studies conducted in China, mental problems do exist comprehensively in caregivers of ALS, and anxiety and depression were associated closely with each other[10; 41]. However, the actual condition was more complicated. Firstly, anxiety was not only seen in caregivers of ALS but was also common in regular populations, especially women in their peri- or postmenopausal period [42]. Based on the results of an epidemiological study of ALS in the Chinese population, the ratio of male patients to female patients in China was about 1.45.1.98:1 [31], which is consistent with our findings. As there were more male patients than female patients in our study, it was speculated that caregivers were mostly women aged 50–70, who had possible risks of being anxious in any event. Traditionally, Chinese women of this age also face the burden of taking care of their grandchildren, making it harder to balance family and their feelings. Secondly, as there was obvious collinearity among anxiety, depression, and quality of sleep, their actual influence on caregiver burden may be overestimated. Even though, non-drug intervention seems to be available and effective for alleviating caregiver burden among caregivers of patients with neuropsychiatric disorders [43; 44]. Similarly, we also observed an evident decline in HAMA scores and HAMD scores after non-drug interventions on caregivers such as psychological counselling classes, professional online communication groups, organizing lectures, and home visits, though a well-designed prospective study should be done to confirm that furtherly.

Limitations

There were four limitations in this study. The sample size was small and respondents could experience remission, so our observational analysis could have been biased. In addition, we failed to assess intervention effects with quantified coping strategies in a prospective study. Another limitation of the study was the lack of information about the patients and the lack of correlations between patients' physical or psychological aspects and caregiver burden. Lastly, this was a study conducted in south-eastern China, and caregivers may only represent a part of the Chinese population.

5. Conclusion

In conclusion, our study demonstrates that caregiver burden is positively correlated with the degree of fatigue and negatively correlated with social support. Low educational status could increase caregiver burden. Caregivers of ALS patients may suffer less from caregiver burden when the patient of ALS was younger and less severe.

- Figure 1 Correlations among caregiver burden and continuous variables
- Figure 2 Correlations between caregiver burden and categorical variables
- **Figure 3** Relationship between α and MSE
- Figure 4 Linear regression between caregiver burden and FS-14

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5	394	Footnotes
7	395	Contributions
, 8	396	Drafting of the manuscript and data analysis: LL Data collection and follow nations: MVZ Formal
9	397	analysis: RIH Paper editing and submission: INI, Validation: WNC Direct guidance paper
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11	399	All authors commented on previous versions of the manuscript and approved the final manuscript.
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36	419	Patient consent for publication
37 38	420	Not required.
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40	499	Ethics Statement
41	122	Ethics Statement
42	423	As this retrospective study is an analysis of existing data, which does not involve patients' or
45 44	424 495	caregivers' diagnosis and treatment, no ethics approval is required from the Ethics Committee of
45	426	fully informed and consent was obtained
46	120	Tuny mornica and consent was obtained.
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48 49	428	Data sharing statement
50	429	Data are available upon reasonable request. The data that support the findings of this study are
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9 10 11 12 13 14	565 566 567 568 569	Acknowledgments We thank all patients and their caregivers of ALS for taking part in this research. We gratefully acknowledge the contribution of the doctors, nurses, and other colleagues during the study.
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Caregiver burden -

Duration(months) -

Social support

PSQI -

FS-14 -

Anxiety -

Depression -



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BMJ Open

Analysing the influencing factors on caregivers' burden among amyotrophic lateral sclerosis patients in China: a cross-sectional study based on data mining

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Primary Subject Heading :	Neurology
Secondary Subject Heading:	Mental health, Palliative care
Keywords:	NEUROLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PSYCHIATRY

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2	1	Title page
4	1	The page
5 6	2	Article
7 8	3	Analysing the influencing factors on caregivers'
9 10	4	burden among amyotrophic lateral sclerosis patients
11 12	5	in China: a cross-sectional study based on data
13 14	6	mining
15 16 17	7 8	Ling Lian ¹ , Minying Zheng ¹ , Ruojie He ¹ , Jianing Lin ^{1,} Weineng Chen ¹ , Zhong Pei ¹ , and Xiaoli Yao ^{1,*}
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32 33	19	*Correspondence: ¹ Xiaoli Yao, <u>yaoxiaol@mail.sysu.edu.cn;</u> Tel: +8620-87755766-8290; Fax: +8620-87750632;
34	20	
35	21	Abstract:
36	22	Objectives: There is significant burden on caregivers of patients with amyotrophic lateral sclerosis
3/	23	(ALS). However, only a few studies have focused on caregivers, and traditional research methods
39	24	have obvious shortcomings in dealing with multiple influencing factors. This study was designed to
40	$\frac{20}{26}$	explore influencing factors on caregiver burden among ALS patients and their caregivers from a new
41	$\frac{20}{27}$	Design: Cross-sectional study
42	28	Setting: The data were collected at an affiliated hospital in Guangzhou, Guangdong, China.
43 44	29	Participants: Fifty-seven pairs of patients with ALS and their caregivers were investigated by
45	30	standardised questionnaires.
46	31	Main outcome measures: This study primarily assessed the influencing factor of caregiver burden
47	32	including age, gender, education level, economic status, anxiety, depression, social support, fatigue,
48	33	sleep quality and stage of disease through data mining. Statistical analysis was performed using SPSS
49 50	34 35	24.0, and LASSO regression model was established by python 3.8.1 to minimize the effect of
51	36	Results: According to LASSO model, we found ten variables had weights. Among them MITOS
52	37	stage(0-1) had the highest weight (-12.235), followed by younger age group(-3.198), lower-educated
53	38	group (2.136), fatigue(1.687), and social support(-0.45). Variables including sleep quality, anxiety,
54 55	39	depression, and sex(man) had moderate weights in this model. Economic status(common), economic
56	40	status(better) ,household(city), household(village), educational level(high), sex(female), age(older),
57	41	MITOS stage(2-4), had a weight of zero.
58	42	Conclusions : Our study demonstrates that the severity of ALS patients is the most influencing factor
59	43	in caregiver burden. Caregivers of ALS patients may suffer less from caregiver burden when the
60	$\frac{44}{45}$	caregiver burden. Caregiver burden is positively correlated with the degree of fatigue and negatively

1 2		
3 4 5	46 47	correlated with social support. Hopefully, more attention should be paid to caregivers of ALS and effective interventions can be developed to relieve this burden.
6 7	48	Keywords: ALS; caregiver burden; LASSO; social support; MITOS; fatigue
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Strengths and limitations of this study

- ♦ This was the first time we study influencing factors on caregiver burden among ALS patients and their caregivers through data-mining based on LASSO regression.
- ♦ The research method solves the problem of small sample size and multicollinearity among independent variables.
- ♦ Different kinds of continuous variables and categorical variables were involved in the study.
- 59 ♦ This was a study conducted in south-eastern China, which may only represent a part of the 60 Chinese population.
 - ♦ Our analysis did not include intervention effects with quantified coping strategies in a prospective study.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with progressive muscle weakness, dysarthria, dyspnoea, dysphagia, and other associated symptoms which prevent patients from taking care of themselves. Patients become increasingly dependent on their partners, family members, and other relatives for increasing support and assistance. For one thing, the high cost of medical care, drugs, and other supportive services exert huge pressure on families with ALS patients. Moreover, the influence on family in caregiving of patients with ALS is great¹². The role of caregivers is critical because their health and well-being are not only important for patients^{3 4}. Moreover, as the disease progresses, patients will suffer from worsening health and diminishing quality of life. Thus, as the disease progresses, the concomitant psychological distress and mental stress of informal caregivers of ALS increase significantly⁵. This phenomenon has also been observed in other neurodegenerative diseases⁶⁷. Kim et al. found a negative correlation between the time spent in caregiving and quality of life of caregivers⁸. In Burke's study, patients' cognitive and behavioural status is of great importance as mediators of caregiver burden⁹. While these studies have demonstrated factors that were associated with an increasing burden for caregivers, we only found a few studies that have focussed on influencing factors of caregivers, such as physical health, psychological symptoms, social background, social support, and the patients' condition, and most of them were designed as cross-sectional studies or case-control studies¹⁰⁻¹⁵. Also, knowledge about the action of interventions in relieving caregiver burden is still limited.

83 This study aimed to determine the effect of factors that influence caregivers' burden and physical 84 and mental health through data mining based on LASSO regression model. Hopefully, effective 85 interventions can be developed to improve the health status of caregivers and help relieve caregiver 86 burden.

88 2. Materials and Methods

89 2.1 Resource of data and participants

Caregivers of patients registered at First affiliated hospital of Sun yat-sen University(FAH-SYSU) from August 2015 to February 2017 and with a patient diagnosis of ALS according to the revised El Escorial criteria were recruited in the study. As this cross-sectional study was an analysis of existing data, which did not involve patients' or caregivers' diagnosis and treatment, no ethics approval was required from the Ethics Committee of FAH-SYSU. Even though, participants enrolled have been fully informed and consent was obtained. The informed consent claimed that the both the patients and their caregivers knew and agreed that their medical records was used in the study anonymously. Healthy caregivers with at least 3 months' caregiving experience were included in the study, and caregivers were restricted to relatives such as spouses, parents, children, and siblings of the patients. Informal, casual, or multiple caregivers and those with confirmed physical and mental problems excluded. Patients who were had rapid deterioration since diagnosis or with bulbar/spinal/respiratory breakdown were excluded from the sample.

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3	102	This study, primarily accessed the influencing factor of arregiver hurden including ago, conden
4	102	education level economic status anyiety depression social support fatigue sleen quality as well as
5	104	the duration and stage of disease(MITOS stage). The quantitative questionnaires of standardised
6	105	design assessed caregiver burden on different dimensions. Standardised scales were used for the
/	106	caregivers, listed in the following section. In total, 60 caregivers of ALS patients were selected for the
0 0	107	survey through internationally accepted questionnaires. Among all the 60 questionnaires sent out to
10	108	the caregivers, 57 valid responses were received, with a valid rate of 95%.
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12	109	2.1.1 Patient and public involvement
13	110	Detionts and/or the public ware not involved in the design conduct reporting or
14	110	Fatients and/or the public were not involved in the design, conduct, reporting, or
15	111	dissemination plans of this research.
17	112	
18	119	
19	115	2.2 Assessment measures and data collection
20	114	2.2.1 Patients' status
21		
22	115	Disease duration was measured by months. Disease severity was mainly measured by the
23	116	clinical staging system of Milano-Torinos (MITOS) ¹⁶ . According to this staging system, patients with
24 25	117	ALS are categorised as follows: Stage 0, functional involvement but no loss of independence in any
25	118	domain; Stages 1-4, which refer to the number of domains in which independence was lost, for
27	119	example, movement, swallowing, communicating, and/or breathing; and Stage 5, death.
28	120	2.2.2 Caregiver burden
29	191	Zanit Canadiuan Pundan Interview (ZPI) was used to evaluate canadiuan hunder 17.18 ZPI consists
31	121 122	of a self-administered 22 item questionnaire, including caregivers' psychological health, finances
32	122 123	emotional wellbeing social and family life and degree of control over their life. Total scores range
33	120	between 0 and 88.
34		
35	125	2.2.3 Social support
30 37	126	The Social Support Rating Scale (SSRS) is a brief questionnaire designed by Xiao Shuiyuan in
38	$120 \\ 127$	1986-1993 which mainly reflects social support and satisfaction with social support from the
39	128	respondents ¹⁹ .
40		
41	129	2.2.4 Physical and mental health of caregivers
42	120	The clean quality of conceivers was accessed using the Dittehungh Clean Quality Index (DCOI)19
43	130	Estimo scale 14 (FS 14) was used to measure the sourity of physical and montal fatigue and its offert
44 45	132	α parson's activities and lifestyle ²⁰ Anxiety and depression status were evaluated using the
46	$132 \\ 133$	Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale-17 (HAMD-17) ^{21,22}
47	100	Trainiton Mixely Scale (Thank) and Trainiton Depression Scale 17 (Thand 17)
48	134	2.3 Statistics
49	125	2.2.1 Company de sus atomisticas
50	130	2.5.1 General characteristics
51	$130 \\ 137$	Statistical analysis was performed using SPSS 24.0 and Fython 3.6.1. Descriptive statistics were
52	138	used for categorical variables. Means with a standard deviation(SD) and interquartile range(IQK)
54	130	performed by Pearson correlation analysis. Correlations between continuous variables were
55	$135 \\ 140$	variables were analysed by visualization analysis. All tests were performed with an alpha value of
56	141	0.05
57	142	
58	143	2.3.2 Least Absolute Shrinkage and Selection Operator (LASSO) regression
59	144	Least Absolute Shrinkage and Selection Operator (LASSO) regression was used to establish a
60	145	model to predict the relationship between caregiver burden and variables with high
	146	multicollinearity. LASSO was a regression technique for variable selection and regularization to

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enhance the prediction accuracy and interpretability of the statistical model that it produces. It was a constrained version of ordinary least-squares (OLS) regression and typically used for regression of a single response variable y on a predictor matrix X, which was widely used in dealing with data situations of low sample size and high dimension, especially when there were both continuous variables and categorical variables in the regression²³.

Compared with other linear regression, lasso was more applicable to analyse complex multicollinear data by adding a penalty equal to the absolute value of the importance of coefficients and minimizing insignificant coefficients to 0, thus the high weight variables will be selected. The absolute size of the regression coefficients β was constrained. The higher the penalty, the more regression coefficients were shrunk toward zero. The regularized regression is quite sensitive to the selection of the penalty coefficients. 24-26

To appropriately tune the best parameter, the approach was to estimate the performance with different values using cross-validation²⁷. Compared with other methods, LASSO was fast and accurate with the advantage of avoiding overfitting automatically.

2.3.3 Prediction Performance Evaluation

 The mean square error (MSE) between the predicted value and the actual value was used to evaluate prediction performance. The coefficient of determination R² was used to reflect the regression fitting effect of the prediction model. The coefficient R^2 is defined as (1 - u/v), where u is the regression sum of squares ((y_true - y_pred) ** 2).sum() and v is the residual sum of squares ((y_true - y_true.mean()) ** 2).sum(). Best possible score is 1.0, and lower values are worse. Lasso best(alpha) parameter was obtained by cross-validation (CV).

The algorithms were implemented using the Lasso CV package of sklearn in Python 3.8.1.

2.4 Data processing and dummy variables

In order to incorporate categorical variables and continuous variables into the LASSO regression model, each variable was processed according to the research purpose. Since continuous variable "age" followed a skewed distribution by calculation of skewness and kurtosis, age was categorized into two groups as categorical variables. Categorical variables were reclassified and served as dummy variables to make the regression result with a positively explanative sense.

Dummy coding method represents group membership with dummy variables that take on values 0 and 1, meaning that membership in a particular group is coded one whereas non-membership in the group is coded zero. When dummy coding is used in the regression analysis, the overall results indicate whether there is a relationship between the dummy variables and the dependent variables²⁸. The values of the intercept and the regression coefficients of the resulted regression model can be obtained using least squares estimation procedures. The coefficient of multiple determination, R², for the regression model with dummy variables can be interpreted in terms of the proportion of variance in the dependent variable that is accounted for by the categorical independent variable²⁹. The regression model from the dummy coding can be written as:

$$Y_{ij} = B_0 + \sum_{j=1}^{k-1} B_j D_{ij} + \varepsilon_{ij}.$$

Where:

 Y_{ii} : The score on the dependent variable for subject i in group j.

 B_0 : The intercept that represents the mean of the group coded 0 on all the dummy variables. *k*: The number of categories of the independent variable.

 B_i : The regression coefficient associated with the jth group, and it represents the difference between the mean of the group coded 1 on the corresponding dummy variable and the mean of the group coded 0 on all the dummy variables.

 D_{ij} : The numerical value assigned to subject i in the jth group.

 ε_{ii} : The error associated with the ith subject in the jth group.

To be specific, categorical variables were recoded with dummy variables, including 2 dummy variables suggesting age, 2 dummy variables suggesting MITOS stage, 2 dummy variables

suggesting economic status, 2 dummy variables suggesting household, and 2 dummy variables

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200 suggesting educational level(Table 1). The principle of the setting of dummy variables was to 201 equalize numbers between groups and accord with the meaning of each variable value. For 202 example, educational level (low) represented the sum of educational status including illiterate, 203 primary school, middle school, and high school, while educational level(high) represented the sum 204 of educational status including junior college, undergraduate, and master. Overall, 6 continuous 205 variables, together with 12 dummy variables of 6 categorical variables were introduced into the 206 model. 207

Table 1 The variable weight of the LASSO regression and description of dummy variables

Variable	The variable weight of LASSO	Description
	regression	
Continuous variables		
Duration	0.077	
PSQI	0.078	
FS-14	1.687	
Anxiety	0.043	
Depression	0.004	
Social support	-0.455	
Categorical variables		
Sex(male)	-0.171	
Sex(female)	0	
Age(younger)	-3.198	<35
Age(older)	0	≥35
MITOS(stage 0-1)	-12.235	MITOS stage 0,1
MITOS(stage 2-4)	0	MITOS stage 2,3,4
Economic status(common)	0	poor, average
Economic status(better)	0	good, excellent
Household(village)	0	suburban, rural
Household(city)	0	city
Educational level(low)	2.136	illiterate
× ,		primary school
		middle school
		high school
		technical secondary school
Educational level(high)	0	iunior college
	-	undergraduate
		master

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212 3. Results

213 3.1 Descriptive analysis of characteristics of caregivers and ALS patients

214 The majority of this cohort was two-thirds female caregivers (38, 66.7 %), and the other one-215third were male caregivers (19, 33.3%). The mean age of all the caregivers was 45.32±13.74 216 years(IQR: 33.5-56.5), ranging from 22-72 years. The average disease course was 28.98±15.36 217 months(interquartile range, IQR: 18-36), with the longest being 60 months and the shortest being 6 55 218 months. The average score of caregiver burden scale was 39.28±17.11(IQR:25-55). The average 56 219 scores of PSQI and FS-14 were 7.89±4.57(IQR:4-10), 6.58±3.60(IQR:4-9), respectively. The average 57 58 220 HAMA scores of patients were 10.70±6.62(IQR:5-15). The average HAMD scores of patients were 59 221 10.16±8.78(IQR:4-14.5). The mean score of the Social Support Rating Scale was 40.18±7.47(IQR:33.5-60 222 46). Forty caregivers were considered "anxious" to different degrees, and the number of possible, 223 definite, obvious, and severe anxiety status caregivers were 20,15,4,1, respectively. Similarly, 27

caregivers were considered "depressed", and the number of possible, moderate, and severe depression status caregivers were 16,10,1, respectively. For categorical variables, the number of patients with MITOS from zero to stage 4 was 10,16,20,4,7, respectively. Most of the caregivers were junior high school graduates (17, 29.8%). Overall, 34 participants (59.6%) had an education level of at least high school, of which two held a master's degree. Urban dwellers constituted a proportion of 56.1% of all the caregivers, while the rest of the individuals were from suburban or rural areas. Economic status varied from general to good condition among the participants (Table 2).

		Ν	N%			Ν	Nº
gender				MITOS			
	male	19	33.3		stage 0	10	17
	female	38	66.7		stage 1	16	28
education					stage 2	20	35
	illiterate	1	1.8		stage 3	4	7.
	primary school	4	7.0		stage 4	7	12
	middle school	17	29.8				
	technical	1	1.8				
	secondary			economic			
	school			state			
	high school	12	21.1		poor	5	8
	junior college	10	17.5		average	21	36
	undergraduate	10	17.5		good	9	15
	master	2	3.5		excellent	22	38
househol	Rural	18	31.6	Age			
d register							
	suburban	7	12.3		<35	15	26
	city	32	56.1		≥35	42	73
				total		57	10

3.2 Analysis of correlations between continuous variables

Correlations between continuous variables were demonstrated with Heatmap Chart shown in Figure 1. According to Spearman correlation analysis, positive correlations were seen between caregiver burden and independent variables including duration of disease, PSQI scores, degree of fatigue, anxiety, and depression(r=0.52, 0.54, 0.76, 0.71, 0.62, p<0.05), while a negative correlation was noted between caregiver burden and social support(r= -0.41, p<0.05). Interestingly, a slight negative correlation was noticed between social support and PSQI scores, degree of fatigue, and depression(r= -0.33, -0.29, -0.37, p<0.05), indicating that social support could be a protective factor. Strong pairwise positive correlations were seen among PSQI scores, degree of fatigue, anxiety, and depression(p<0.05).

3.3 Analysis of correlations between caregiver burden and categorical variables

Correlations between caregiver burden and categorical variables were shown as visualizations (Figure 2). We used layered data processing to rearrange categorical variables and convert them into dummy variables. The principle of the setting of dummy variables was to equalize numbers between groups. The descriptions of each dummy variable were shown in Table 1. Figure 2 (1) showed that there was a difference in caregiver burden between younger and older patients. Also, an obvious disparity in caregiver burden was seen between group MITOS stage(0-1) and group MITOS stage(2-4), suggesting that patients with ALS with severer symptoms created higher caregiver burden(Figure 2 (5)).

3.4 Model construction and evaluation by Lasso regression

3.4.1 Variable Selection

stage(2-4), had a weight of zero (Table 1).

3.4.2 Performance evaluation

3.5.1 Variable selection

- The values of each categorical attribute were converted into dummy variables to build a regression model. With caregiver burden as the dependent variable and duration, PSQI, FS-14, anxiety, depression, social support, sex(male), sex(female), age(younger), age(older), MITOS stage (0-1), MITOS stage(2-4), economic status(common), economic status(better), household(village), household(city), educational level(low), educational level(high) as independent variables, a regression model with multiple dummy variables was constructed shown in Table 1. In the LASSO model, we found ten variables had weights. Among them, MITOS stage(0-1) had the highest weight (-12.235), followed by younger age group(-3.198), lower-educated group (2.136), fatigue(1.687), and social support(-0.45). Variables including sleep quality, anxiety, depression, and sex(man) had moderate weights in this model. Economic status(common), economic status(better) ,household(city), household(village), educational level(high), sex(female), age(older), MITOS In this research, the mean squared error (MSE) was selected as the evaluation index, and the best Alpha value was obtained through cross-validation. The relationship between the model MSE and Alpha is shown in Figure 3. When the best penalty factor 'Alpha'= 0.3, the MSE is the smallest, and the LASSO regression model has the highest accuracy. To evaluate prediction performance and fitting effect, the R² and the MSE of the LASSO regression model were provided. The Lasso score(R²) and the lasso MSE were 0.831 and 48.496, respectively. 3.5 Liner regression analysis between MITOS stage(0-1), FS-14, and caregiver burden In the previous section, we learned from the LASSO regression model that MITOS stage(0-1) had the highest weight among categorical variables, while FS-14 had the highest weight among continuous variables. Moreover, the coefficient of MITOS stage(0-1) was significantly higher than
- other influential dummy variables, and the coefficient of FS-14 was even hundreds of times higher than other continuous variables. Therefore, to furtherly validated the action of the most influential factors in the model, a linear regression model was constructed with caregiver burden as the dependent variable, and FS-14, MITOS stage (0-1) as independent variables. 3.5.2 Performance evaluation As was shown in Figure 4, caregiver burden was positively correlated with FS-14 whenever dummy variable MITOS stage(0-1) was kept in the model or not. On the other hand, when FS-14 remained constant, caregiver burden was significantly higher when dummy variable MITOS stage(0-1) was absent. The distance between the red line and the green line demonstrated the
- influence of MITOS stage(0-1) on caregiver burden in the model. The intercepts of the linear regression model was 32.125. The Lasso score(R^2) and the lasso MSE were 0.783 and 62.46, respectively. The results were consistent with LASSO regression, suggesting that MITOS stage(0-1) had a strong effect on caregiver burden.

4. Discussion

Based on the LASSO model, 10 variables had weights, whereas 5 variables had a greater influence on the model. MITOS stage(0-1) had the highest weight (-12.235), followed by younger age group(-3.198), lower-educated group (2.136), fatigue(1.687), and social support(-0.45). According to the results mentioned above, MITOS stage of patients with ALS was the most important factor influencing caregiver burden, and caregiver burden was significantly lower in patients of ALS with a milder type (MITO stage 0-1). Interestingly, when another variable duration of disease was brought into the regression model, it didn't show any effect on the model, indicating that compared to duration, the severity of patients with ALS had a greater influence on caregiver

burden. Sarah K. Bublitz found that thick mucus was a highly distressing symptom for both
 patients and caregivers, which caused a higher degree of bulbar impairment and had a strong
 impact on their quality of life³⁰.

We draw a conclusion from our study that caregiver burden was positively correlated with the degree of fatigue, while the correlation between caregiver burden and psychological factors such as anxiety and depression was relatively weak. The research of Brizzi K T et.al also showed that the pressure of caregiving in ALS originated from physical symptoms consisting of fatigue, pain, weakness, shortness of breath, difficulty sleeping, and speech problems, as well as depression and other mood changes. It was worth noting that fatigue and weakness were the most common symptoms and happened in over 75% of respondents ³¹, which was in accordance with our study. In our LASSO model, fatigue had higher weights than anxiety, depression, and sleep quality. Physical exhaustion was also a typical feature of caregiver burden of other progressive diseases, such as Alzheimer's disease, Parkinson's disease, and cancer³²⁻³⁵. Not surprisingly, the feelings of fatigue probably came from long-distance travel to the hospital for treatment, strenuous work in caregiving, and loss of rest time. This could well explain our result that younger caregivers suffered less from caregiver burden because they were healthier and more energetic, although they needed to consider time-consuming costs and balance between work and caring. For those younger caregivers, their caring patients were also younger as most of the caregivers were their spouses. This could be another reason that younger caregivers experienced less caregiver burden.

In this study, we found that caregiver burden was negatively correlated with social support, which was consistent with a study in Korea ³⁶. According to the epidemiology of ALS in China, we have a potentially lower incidence and prevalence of ALS than in foreign countries ³⁷. It is still a rare disease so doctors with less experience may fail to make a correct diagnosis in time and provide appropriate treatment. Even if the diagnosis is clear, effective treatment is not always available to every family due to the high cost of treating the illness. Fortunately, ALS is gradually being covered by health insurance in many provinces of China. The guarantee of a new policy is of great importance in helping relieve the economic burden on caregivers. In addition to economic support, more attention was paid to this group because of increasing caring activities, media reports, and social propaganda such as the "Ice Bucket Challenge" all over the country³⁸. Multiple-center clinical studies of potential drugs based on animal experiments have also been conducted by a great number of Chinese research teams ^{39 40}, bringing hope and light to patients and caregivers of ALS.

On the other hand, according to our study, social support only had a modest action on caregiver burden. This phenomenon might be caused by insufficient and unbalanced social support in China. Therefore, we speculated that greater social support would bring about less caregiver burden. In some well-developed regions such as Hong Kong, the promotion of multidisciplinary teams (MDT) provides effective support for the disease, which encourages patients and families of ALS in a highly positive manner⁴¹. Family care is the main strategy for Chinese caregivers to look after ALS patients, and older women and spouses still play an important role in providing family care, while in some other countries, hospital care, nursing home care, and community care were made full use of to help alleviate the families' burden ^{42 43}. The lack of professional caring experience, staff, and facilities could affect the efficiency of caring and thus lead to an increasing caregiver burden. Although China has developed rapidly in recent years, there have been obvious differences in medical development and medical investments between eastern and western areas. Little research on ALS has been conducted in western areas, where economic conditions are relatively poor and social support is inadequate. In contrast, modern countries, such as Japan and other European countries can offer stronger social aid and help systems to ALS families through long-term care insurance, home visit rehabilitation, and peer group rehabilitation, suggesting that more social support could be provided to Chinese ALS caregivers to relieve their burden ¹³ ⁴³⁻⁴⁶. In addition, medical expenses and end-of-life care were guaranteed in well-developed countries like Japan. Obviously, there is an urgent need for more economical, practical, physical, emotional, and spiritual support for caregivers of ALS.

350350It was surprising to find in our study that educational level influenced caregiver burden. In this60351study, caregivers of ALS patients were mainly their spouses who were of the same age (50-70y) and352had similar educational levels (middle school) to the patients. A possible explanation is that

understanding abilities varied among different caregivers and could be a limitation in low-educated groups. Under the current situation in China, patients were not able to address all their questions in a short period because of the large hospital outpatient quotas. For those caregivers who had a lower educational level, they might feel difficult to quickly understand the key points in caring and follow doctors' suggestions. In addition, they possibly lacked the abilities to search for information and teach themselves to improve the efficiency of home nursing work.

We investigated the correlations between caregiver burden and caregivers' mental states, including anxiety, depression, sleep quality index, and fatigue. Although we observed a slight correlation between anxiety, depression, and caregiver burden, they didn't show high weights in the LASSO regression model as we expected. In contrast with other studies conducted in China, mental problems do exist comprehensively in caregivers of ALS, and anxiety and depression were associated closely with each other¹⁰⁴⁷. However, the actual condition was more complicated. Firstly, anxiety was not only seen in caregivers of ALS but was also common in regular populations, especially women in their peri- or postmenopausal period ⁴⁸. Based on the results of an epidemiological study of ALS in the Chinese population, the ratio of male patients to female patients in China was about 1.45.1.98:1 ³⁷, which is consistent with our findings. As there were more male patients than female patients in our study, it was speculated that caregivers were mostly women aged 50–70, who had possible risks of being anxious in any event. Traditionally, Chinese women of this age also face the burden of taking care of their grandchildren, making it harder to balance family and their feelings. Secondly, as there was obvious collinearity among anxiety, depression, and quality of sleep, their actual influence on caregiver burden may be overestimated. Even though, non-drug intervention seems to be available and effective for alleviating caregiver burden among caregivers of patients with neuropsychiatric disorders 49 50.

From the conclusion obtained above, practical actions should be done for healthcare system to help relieve caregiver burden of ALS. Financial assistance and professional nursing guidance, including long-term care insurance, medical investments, professional online communication groups, home visit rehabilitation, nursing home care and community care etc., may be particularly beneficial as part of ALS care^{13 43 45}. Regional ALS centres participated by doctors, nurses, psychologists, rehabilitation trainers, social workers, nutritionists, communities, speech trainers, families, and researchers, are necessary for healthcare system to provide complete and efficient support¹⁰⁵¹. Physical, psychological, emotional, and social support are potential effective non-medication interventions to help relieve caregiver burden^{42 52-54}. Healthcare system should pay more attention to the health status of both the patients and their caregivers proactively. Hopefully, positive and effective strategies can be developed as soon as possible to improve the situation.

Limitations

There were four limitations in this study. The sample size was small and respondents could experience remission, so our observational analysis could have been biased. In addition, we failed to assess intervention effects with quantified coping strategies in a prospective study. Another limitation of the study was the lack of information about the patients and the lack of correlations between patients' physical or psychological aspects and caregiver burden. Lastly, this was a study conducted in south-eastern China, and caregivers may only represent a part of the Chinese population.

5. Conclusion

In conclusion, our study demonstrates that the most influencing factor of caregiver burden is the severity of ALS patient. Caregivers of ALS patients may suffer less from caregiver burden when the patients are less severe and the caregivers are younger. Low educational status could increase caregiver burden. Caregiver burden is positively correlated with the degree of fatigue and negatively correlated with social support.

Figure 1 Correlations among caregiver burden and continuous variables

1 2 3 4	406	Figure 2 Correlations between caregiver burden and categorical variables
5 6	407 408	Figure 3 Relationship between α and MSE Figure 4 Linear regression between caregiver burden and FS-14
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30	432	
31	400	
32	433	Provenance and peer review
33 24	434	Not commissioned; externally peer-reviewed.
34 35	435	
36	436	Patient consent for publication
37 38	437	Not required.
39	438	
40	/30	Ethics Statement
41	100	Etitics Statement
42	440	As this descriptive study is an analysis of existing data, which does not involve patients' or
43	441	caregivers' diagnosis and treatment, no ethics approval is required from the Ethics Committee of
44 45	442	First Affiliated hospital of Sun yat-sen University. Even though, participants enrolled have been
45	443	fully informed and consent was obtained.
40 47	444	
48	445	Data sharing statement
49	446	Data are available upon reasonable request. The data that support the findings of this study are
50	447	available from the corresponding author on reasonable request.
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50	613	Acknowledgments				
51	614	We thank all patients and their caregivers of ALS for taking part in this research. We gratefully				
53	615 616	acknowledge the contribution of the doctors, nurses, and other colleagues during the study.				
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STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		line 5
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found line 22-47
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		line 67-82
Objectives	3	State specific objectives, including any prespecified hypotheses line 83-86
Methods		
Study design	4	Present key elements of study design early in the paper line 92
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,
-		exposure, follow-up, and data collection line 90-92,102-104
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of
		participants line 91-92, 97-101
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
		modifiers. Give diagnostic criteria, if applicable <u>NA</u>
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there is
		more than one group line 113-141
Bias	9	Describe any efforts to address potential sources of bias line 107-108
Study size	10	Explain how the study size was arrived at line 106-108
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why line 143-206
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		line 143-206
		(b) Describe any methods used to examine subgroups and interactions line 143-206
		(c) Explain how missing data were addressed <u>NA</u>
		(d) If applicable, describe analytical methods taking account of sampling strategy
		NA
		(e) Describe any sensitivity analyses <u>NA</u>
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially
		eligible, examined for eligibility, confirmed eligible, included in the study,
		completing follow-up, and analysed line 107-108
		(b) Give reasons for non-participation at each stage <u>NA</u>
		(c) Consider use of a flow diagram <u>NA</u>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
		information on exposures and potential confounders line 214-232
		(b) Indicate number of participants with missing data for each variable of interest
		<u>line 107-108</u>
Outcome data	15*	Report numbers of outcome events or summary measures table 1
Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
		their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included line 233-250, 251-290

		(b) Report category boundaries when continuous variables were categorized <u>line</u>
		 <u>251-290</u> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses line 251-290
Discussion		
Key results	18	Summarise key results with reference to study objectives line 397-401
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias line 389-395
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence line 292-375
Generalisability	21	Discuss the generalisability (external validity) of the study results line 376-386
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based <u>line 418-428</u>

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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