

ORIGINAL RESEARCH

Trends in health outcomes for family caregivers of hip-fractured elders during the first 12 months after discharge

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Accepted for publication 28 May 2011

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SHYU Y.-I.L., CHEN M.-C., LIANG J. & TSENG M.-Y. (2012) Trends in health outcomes for family caregivers of hip-fractured elders during the first 12 months after discharge. *Journal of Advanced Nursing* 68(3), 658–666. doi: 10.1111/j.1365-2648.2011.05778.x

Abstract

Aim. This article reports on trends in health outcomes for family caregivers of hip-fractured patients and the effects of social support on these outcomes.

Background. Little is known about the impact of caregiving on the health outcomes of family caregivers of patients with hip fracture.

Method. For this prospective, correlational study, data were collected from 135 family caregivers of hip-fractured elders (2001–2005). Data on health-related quality of life and social support were collected from family caregivers at 1, 3, 6 and 12 months after discharge of the older hip-fractured patient.

Findings. During the 12 months after the patients' discharge, family caregivers' scores improved significantly in role performance-related scales, including bodily pain, social function, role limitations due to emotional problems and role limitations due to physical problems. However, caregivers' scores for general health and mental health were significantly lower at 12 months [59.91 (SD = 24.54) and 65.91 (SD = 14.36) respectively] than at 1 month after discharge [64.35 (SD = 23.29) and 67.94 (SD = 18.47) respectively]. The trends for most subscale scores for health-related quality of life were positively related to perceived availability of social support.

Conclusions. Caring for a hip-fractured older family member over a sustained period may enhance family caregivers' role performance, but have a negative impact on their perceived general health and mental health. These results suggest that home care nurses should develop interventions early after discharge to assess and improve family caregivers' health perception, mental health and social support.

Keywords: caregivers, family care, hip fracture, mental health, nursing, quality of life

Introduction

As the population aged 65 and over is increasing rapidly, hip fracture has become a major health crisis for the older adult

population in Taiwan, similar to many other countries. Hip fracture in Taiwan had an age-adjusted incidence rate (per 100,000) from 1996 to 2000 of 225 for men and 505 for women (Chie *et al.* 2004). Older people not only suffered a

sustained decline in physical function early after hip fracture, but a large per cent (26–76%) who survived the first or even second year following hip fracture also failed to recover function (Norton *et al.* 2000, Shyu *et al.* 2004a). In the current era of shorter hospital stays, family care has been a less expensive alternative to the extensive use of intermediate care facilities after hospital discharge (Williams *et al.* 1996). Family caregivers offer both practical help and psychological support to patients with hip fracture during their rehabilitation (Macleod *et al.* 2005). However, little is known about family caregivers of hip-fractured elders compared with the abundant literature on family caregivers of older adults suffering from stroke or dementia (Argimon *et al.* 2004, Ablitt *et al.* 2009, Rigby *et al.* 2009, Saban *et al.* 2010).

Family caregivers of hip-fractured patients were reported to spend the largest amount of time and energy in 1 month after discharge, when they also encountered most of the problems (Williams *et al.* 1996) and experienced moderate burden (Lin & Lu 2005). Furthermore, caregiver burden was negatively related to the physical function of the older patient with hip fracture (Lin & Lu 2007). Caregiver burden at 1 month after hospital discharge was predicted by burden at 1 week and extent of social support (Lin & Lu 2007). However, no studies were found on the health outcomes of these family caregivers. These health outcomes need to be taken into consideration by healthcare providers, while examining the cost and impact of hip fracture. In particular, trends in health outcomes of family caregivers during the critical recovery period for hip-fractured elders after hospital discharge offer important information for developing transitional care protocols.

On the other hand, social support has been associated with less caregiver burden (Weitzner *et al.* 1999, Chang *et al.* 2001, Lin & Lu 2007). However, the role of social support on health outcomes has not been explored for family caregivers of hip-fractured elders. Therefore, when examining the impact of caring for a hip-fractured elder on caregivers' health outcomes, it is also necessary to consider the effect of caregivers' social support.

Background

Little information was found regarding family caregivers of patients with hip fracture. In one study, family caregivers of hip-fractured patients spent the most time and energy and encountered the most problems when caregiving at 2 weeks after discharge compared with 8 and 14 weeks (Williams *et al.* 1996). In a more recent study in Taiwan, the burden of family caregivers ($N = 98$) in the first month after hospital discharge of patients with hip fracture was moderate and

negatively correlated with patients' functional level (Lin & Lu 2005). However, the health outcomes of these family caregivers were not explored. As family caregiver's needs, health outcomes and quality of family care were important, predictors for hospital readmission and institutionalization (Shyu & Lee 2002, Shyu *et al.* 2004b), and understanding the impact of caregiving on the health outcomes of family caregivers for patients with hip fracture is important for clinical practice.

Interventions on improving social support for family caregivers of older adults were found to effectively increase caregivers' confidence, coping ability and caregiver outcomes (Stewart *et al.* 1998, Pillemer *et al.* 2003). However, no studies were found on the role of social support on health outcomes of family caregivers for a family member with hip fracture.

The context of family caregiving in Taiwan is substantially different from that in western countries. The majority of the older people in Taiwan (64.3%) live with their children, whereas only one-fifth and one-quarter of the old people live with an adult child in the United States of America (USA) and Europe respectively (Ministry of the Interior, Republic of China 2006, Pezzin *et al.* 2007). Since the implementation of National Health Insurance in 1995, pressures to contain costs and reimbursement regulations have challenged hospitals to minimize their costs and to maximize profits by moving patients out of the hospital as soon as medically possible. Thus, family caregivers are under more stress in taking care of their discharged older family members. Chinese culture and social orientation emphasizes devotion to parents and interdependence (Dai & Dimond 1998). These societal norms about family relationships may cause extra burden for family caregivers in Taiwan. In addition, the underdevelopment of community- and home-based long-term care resources (Wu & Chuang 2001) creates further difficulties for family caregivers in Taiwan. Therefore, studies conducted in western countries regarding family caregivers of patients with hip fracture need to be further explored and validated in Taiwan.

The study

Aims

The first aim of this study was to describe trends in health outcomes for family caregivers of hip-fractured patients during the first 12 months following hospital discharge. The second aim was to explore the effect of perceived availability of social support on trends in health outcomes for family caregivers.

Design

A prospective, correlational study design was used.

Participants

A convenience sample of family caregivers of older adults with hip fracture was recruited from a 3000-bed medical centre in northern Taiwan. Inclusion criteria for hip-fractured elders were: (i) aged 65 years or older, (ii) hospitalized for surgical internal fixation or arthroplasty after hip fracture, (iii) living in northern Taiwan and (iv) independent in activities of daily life [ADL; Chinese Barthel Index (Chen *et al.* 1995), CBI ≥ 70] before the fracture. The inclusion criterion for previously independent elders was selected to exclude the impact of other disabilities on caregiver health outcomes, thus limiting the impact to hip fracture. Inclusion criteria for family caregivers were: (i) age 18 years or older, and (ii) assuming primary responsibility for providing direct care or supervising the care received by the patient. A sample size of 84–110 was estimated based on preliminary data showing Pearson's correlation coefficient of 0.3 between social support and health-related quality of life, significance level of 0.05 and power between 0.80 and 0.90.

Data collection

Among the 451 patients who met our sampling criteria, 151 were interested in participating in the study. The main reason for not being interested in participation was that the patient or family members did not want to be bothered. Of these 151 patients, 25 refused home visits and one died the day after discharge. In the final sample, 135 family caregivers were enrolled in the study and interviewed at 1 month after discharge. Data were collected over a 4-year period (2001–2005). During this period, the factors that might influence the health outcomes of patients and family caregivers did not change. These factors included treatment modality, health insurance and postdischarge community health services. Of the 135 patients, 122 (90.4%) were interviewed at 3 months, 116 (85.9%) at 6 months and 98 (72.6%) at 12 months after patient discharge. Attrition was due to loss of contact and refusal to participate.

Ethical considerations

Before data collection, the institutional review board of the medical centre approved the study. Research assistants identified potential family caregivers and invited them to participate in this study. Family caregivers and patients who

agreed to participate signed informed consent and were interviewed face-to-face in their homes at 1, 3, 6 and 12 months after the patient's discharge.

Instruments

Medical Outcomes Study (MOS) Social Support Survey

Social support was measured at 1 month after patient discharge using the MOS Social Support Survey, Taiwan version (Shyu *et al.* 2006). This instrument has 19 functional support items originally hypothesized to measure availability of emotional support (four items), informational support (four items), tangible support (four items) and affectionate support (three items), and positive social interactions (four items) (Sherbourne & Stewart 1991). For each subscale, the score is averaged across items. These scores are then averaged for an overall support index, which is then transformed to 0–100, with higher scores indicating more availability of support (Sherbourne & Stewart 1991). The overall summary scores can range from 19 to 95, with higher scores indicating more social support. The reliability and validity of this scale has been established in a Taiwanese sample (Shyu *et al.* 2006). In this study, Cronbach's alpha of MOS social support survey was 0.97.

MOS SF-36

Different dimensions of family caregivers' perceived health outcomes were measured using the MOS SF-36, Taiwan version (Lu *et al.* 2003, Tseng *et al.* 2003). The SF-36 measures concepts of physical functioning (10 items), role limitations due to physical health problems (RP) (four items), bodily pain (BP) (two items), general health (five items), vitality (four items), social functioning (SF) (two items), role limitations due to emotional problems (RE) (three items) and mental health (five items). Raw scale scores are transformed into a scale of 0–100. Higher scores imply better health-related quality of life. The Taiwan version of the MOS SF-36 has been shown to have good validity and reliability (Lu *et al.* 2003, Tseng *et al.* 2003). In this study, Cronbach's alphas of the MOS SF-36 ranged from 0.51 to 0.97, with only three of 32 under 0.70.

Chinese Barthel Index

The CBI (Chen *et al.* 1995) was used to assess hip-fractured elders' physical functioning, including dependencies in eating, transferring, grooming, toileting, bathing, walking, climbing stairs, dressing and bowel and bladder control. Patients' CBI scores were assessed at the same time as the family caregivers' health outcomes. The CBI has been used with good reliability and validity in studies of Taiwanese patients with hip fracture

(Shyu *et al.* 2004a). In this study, Cronbach's alpha for the CBI was 0.93.

Data analysis

The generalized estimating equation (GEE) (Liang & Zeger 1986, 1993) approach was used to examine changes in family caregivers' health outcomes and to determine whether perceived availability of social support predicted the trends in these health outcomes during the first year following hospital discharge. The GEE approach was used to model dependent dichotomous variables (eight dimensions of SF-36) as a function of time, social support and covariates (family caregivers' age, gender, marital status and educational background, as well as patients' dependency in ADL). All data were analysed using SAS Win 8.0 (Cary, NC, USA) computer software.

Results

Sample characteristics

Caregivers in this sample tended to be women (57.8%), had an average age of 52.8 years ($SD = 12.69$), and were mostly married (88.7%). Around one-third (32.6%) were sons, 26.7% were daughters-in-law, 20% were spouses and 14.1% were daughters. Caregivers' average overall social support score was 68.34 ($SD = 17.09$), representing moderately good availability of perceived support. The subscale scores were 75.64 ($SD = 20.26$) for tangible support, 69.78 ($SD = 21.22$) for emotional support, 70.32 ($SD = 20.06$) for affectionate support, 67.57 ($SD = 22.76$) for positive interaction and 72.29 ($SD = 19.11$) for informational support, indicating moderately good perceived support.

The older patients with hip fracture were mostly women (66.7%), and had an average age of 78.3 years ($SD = 7.78$). The majority of patients (57%) had femoral neck fracture, 37% had intertrochanteric fracture and 6% had subtrochanteric fracture, with 87 (64.4%) receiving internal fixation and 48 (35.6%) receiving arthroplasty. Patients had an average prefracture CBI of 96 ($SD = 6.55$), and an average CBI of 77.15 ($SD = 17.96$) at 1 month after discharge. Most hip-fractured elders lived with their family members or only with their spouse before admission ($n = 124$, 92.6%), at 1 month (96.3%), 3 months (97.5%), 6 months (99.1%) and 12 months (97.9%) after discharge.

Comparison of caregivers' health outcomes with the norm

To provide an overview, we compared the average scores of the eight SF-36 subscales for family caregivers of hip-

fractured elders during the 12 months after discharge with a norm of healthy 45- to 54-year-old adults in the community (Tseng *et al.* 2003) (Figure 1). At the first month after patient discharge, family caregivers' vitality, mental health, physical function and physical role appeared to be poorer than those for the norm. The performance on most subscales improved as more time passed since the patient's discharge. Family caregivers of hip-fractured elders had similar health outcomes as the norm at 12 months after the patient's discharge, except that mean vitality (63.79, $SD = 15.85$) and mental health (65.91, $SD = 14.36$) were still poorer than those for the norm (vitality = 68.19, $SD = 18.96$ and mental health = 74.09, $SD = 17.57$). On the other hand, caregivers' mean score for RE (86.68, $SD = 27.54$) was better than that for the norm (82.36, $SD = 34.00$).

Trends in health outcomes

Changes in scores on the eight SF-36 subscales over the 12 months after hospital discharge are presented in Figure 2. Among all subscale scores, the poorest performance was in health outcomes related to caregivers' perceptions, i.e., general health, vitality and mental health. On the other hand, caregivers scored better on role performance-related health outcomes such as BP, social function, RE and role limitations due to physical problems. The mean scores for each subscale at each time point are listed in Table 1.

Generalized estimating equation analysis showed that role performance-related subscales (BP, SF, RE and RP) improved significantly during the 12 months after hospital discharge. Furthermore, the health outcomes (scores) of these subscales

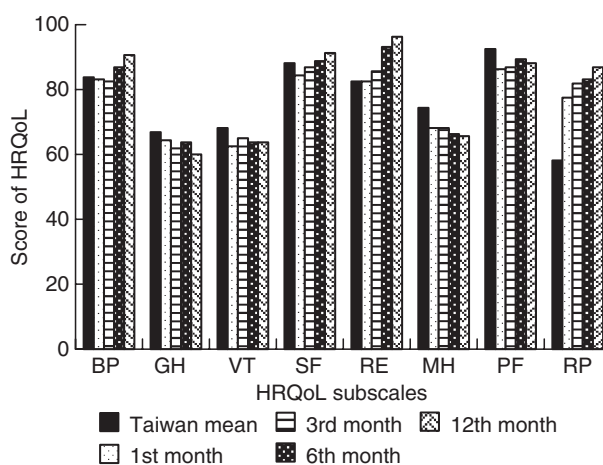


Figure 1 HRQoL of caregivers for hip-fractured elders compared with the age-matched norm data for the norm were drawn from Tseng *et al.* (2003). HRQoL, health-related quality of life.

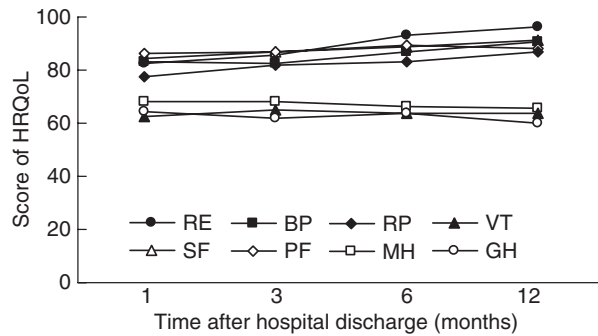


Figure 2 Trends in HRQoL for caregivers of hip-fractured elders in the first year after patients' hospital discharge. HRQoL, health-related quality of life.

were significantly better at 12 months after discharge than at 1 month after discharge, i.e. at 12 months, BP was 90.53 (SD = 19.26), SF was 91.12 (SD = 13.74), RE was 96.26 (SD = 16.08) and RP was 86.68 (SD = 27.54), whereas at 1 month, BP was 83.08 (SD = 20.76), SF was 84.25 (SD = 19.79), RE was 82.71 (SD = 33.29) and RP was 77.59 (SD = 35.91). Health outcomes for BP and RE were significantly better at 6 months after discharge than at 1 month after discharge, i.e., at 12 months BP was 86.95 (SD = 20.51) and RE was 93.10 (SD = 23.47), whereas at 1 month BP was 83.08 (SD = 20.76) and RE was 82.71 (SD = 33.29). In other words, BP and RE improved significantly between the first

and sixth month after discharge, whereas social function and role limitations due to physical problems improved gradually over the 12-month period.

Caregivers' general health and mental health declined gradually, but significantly during the 12 months after discharge. Health outcomes for these two subscales were significantly poorer at 12 months after discharge than at 1 month after discharge, i.e., at 12 months GH was 59.91 (SD = 24.54) and MH was 65.91 (SD = 14.36), whereas at 1 month GH was 64.35 (SD = 23.29) and MH was 67.94 (SD = 18.47), but not at other times. Vitality and physical performance remained stable throughout the 12 months after discharge.

Influences of social support and patients' dependency in ADL

The changes over time in most SF-36 subscale scores were positively related to social support after controlling for covariates (Table 1), meaning that the better the family caregiver's perceived availability of social support at 1 month after discharge, the better their health outcomes in all dimensions during the first 12 months after the patient's discharge. However, the trends in family caregivers' health outcomes were not impacted by changes in patients' dependency in ADL.

Table 1 Trends in caregiver health outcomes and influence of social support during the first year after patient discharge.

Health-outcome dimension	Time after patient discharge, mean (SD) (P)				Social support, β (P)	Patients' ADL, β (P)
	1 month	3 months	6 months	12 months		
Bodily pain (BP)	83.08 (20.76) (Baseline)	82.46 (24.10) (0.94)	86.95 (20.51) (0.01)	90.53 (19.26) (0.01)	0.274 (0.01)	-0.067 (0.23)
General health (GH)	64.35 (23.29) (Baseline)	62.13 (25.13) (0.27)	63.47 (23.56) (0.64)	59.91 (24.54) (0.05)	0.416 (0.01)	0.011 (0.86)
Vitality (VT)	62.29 (20.32) (Baseline)	64.92 (19.88) (0.35)	63.84 (18.63) (0.64)	63.79 (15.85) (0.81)	0.352 (0.01)	-0.002 (0.95)
Social functioning (SF)	84.25 (19.79) (Baseline)	86.69 (19.04) (0.38)	88.79 (18.97) (0.08)	91.12 (13.74) (0.01)	0.222 (0.01)	0.002 (0.95)
Role limitations due to emotional problems (RE)	82.71 (33.29) (Baseline)	85.37 (32.26) (0.50)	93.10 (23.47) (0.01)	96.26 (16.08) (0.01)	0.414 (0.01)	0.001 (0.99)
Mental health (MH)	67.94 (18.47) (Baseline)	68.00 (18.22) (0.45)	66.21 (18.75) (0.22)	65.91 (14.36) (0.08)	0.358 (0.01)	-0.020 (0.62)
Physical functioning (PF)	86.11 (23.17) (Baseline)	87.14 (20.06) (0.44)	89.61 (18.87) (0.06)	88.08 (19.51) (0.27)	0.181 (0.02)	-0.060 (0.33)
Role limitations due to physical health problems (RP)	77.59 (35.91) (Baseline)	82.06 (31.97) (0.22)	82.97 (32.07) (0.11)	86.68 (27.54) (0.02)	0.353 (< 0.01)	-0.002 (0.98)

P values were obtained by GEE analysis of health outcomes relative to baseline after controlling for social support, family caregivers' age, gender, marital status and educational background and patients' dependency in activities of daily living (ADL). GEE, generalized estimating equation.

Discussion

Limitations of the study

This study is the first to describe trends in health outcomes for family caregivers of hip-fractured elders in Taiwan, but was limited by no data on prefracture health outcomes of family caregivers, use of a convenience sample using data collected more than 5 years ago and lack of a true control population. The impact of using a convenience sample on generalizability of the results might have been minimized by the similarity in age, gender and marital status of our sample to those of a national representative sample of family caregivers in Taiwan (Wu & Lin 1999) and a sample of family caregivers for patients with hip fracture in Taiwan (Lin & Lu 2005). We believe that the data from this study are still relevant today for two reasons. First, despite a lack of more recent studies on family caregivers of patients with hip fracture, the profile of the patients with hip fracture in our study sample was similar to that of their counterparts in a recent study (Lin *et al.* 2010). Second, postdischarge community services for families of patients with hip fracture have remained the same during the past 10 years (Department of Health 2010). Finally, the number of family caregivers in the comparator group of healthy 45- to 54-year-old adults in the community (Tseng *et al.* 2003) was not surveyed. Thus, the impact of caregiving for patients with hip fracture on the health of family caregivers when compared with their counterparts in the general population might be underestimated.

Discussion of results

Our study results showed that caregivers' vitality, mental health, physical function and role limitations due to physical problems appeared to be poorer than the norm at 1 month after a patient's discharge, and in particular, vitality and mental health appeared to be poorer than the norm even at 12 months after a patient's discharge. On the other hand, caregivers' role limitations related to emotional function were better than the norm at 12 months after discharge. These results suggest that caregiving had a greater impact on perception-related health outcomes for these family caregivers than on role performance-related outcomes. The responsibility of the caregiver role may enhance a family caregiver's performance regardless of their health perceptions.

In terms of the trends in caregivers' health outcomes, we found that scores on role performance subscales improved, but scores on general health and mental health subscales declined during the 12 months after discharge. Caregivers'

improved role performance might have been due to improved performance of ADL among older persons during the first year following hip fracture (Shyu *et al.* 2004a). This lower dependency in ADL might have decreased caregiving demands, lessened caregiver burden and improved caregiver role performance during this period. Although providing care to a hip-fractured older family member over a sustained period seemed to enhance family caregivers' role performance, this caregiving negatively impacted their health perceptions and mental health. These findings add to the literature, as little information could be found on changes in health outcomes for this population of family caregivers. One study did find that these caregivers encountered a greater impact and more problems at 2 weeks than at 8 and 14 weeks after patient discharge (Williams *et al.* 1996).

We also found an association between social support and health outcomes for family caregivers of hip-fractured older persons in Taiwan, consistent with previous reports on the impact of social support on caregiver burden (Weitzner *et al.* 1999, Chang *et al.* 2001, Lin & Lu 2007). Rather than evaluating the influence of social support at a specific time point, the results of this study expand previous knowledge by showing the influence of social support on the trends in postdischarge health outcomes of family caregivers of hip-fractured patients. By measuring social support at 1 month after discharge and the outcome variables at 1, 3, 6 and 12 months after discharge in this prospective, longitudinal study, we were able to explore causal relationships among these variables. The importance of social support in this sample of caregivers might be explained by the emphasis on interdependence and social orientation in Chinese culture (Dai & Dimond 1998). On the other hand, we found that all types of social support were perceived as moderately available, but emotional and positive-interaction supports were perceived as least available, and tangible support was the most available. These differences might explain why family caregivers' health perceptions and mental health were more impacted and were poor even at 1 year following the patient's discharge.

In terms of covariates, we found that not being married predicted poorer caregiver vitality, poorer social function and poorer role performance influenced by emotional problems. This finding may be explained by previous reports that marriage was positively related to physical health in the United Kingdom (Prior & Hayes 2003) and USA (Schoenborn 2004). However, we found that patients' dependency in ADL did not impact the trends in family caregivers' health outcomes, in contrast to a previous report that the functional level of patients was negatively correlated with caregiver burden (Lin & Lu 2005). This difference might be due to

What is already known about this topic

- Family caregivers of hip-fractured patients spend the most time and energy, encounter the most problems and experience moderate caregiver burden in the first month of patient discharge.
- Social support has been associated with less caregiver burden.

What this paper adds

- Family caregivers for a family member recovering after hip fracture had poorer perception-related health outcomes, including general health, vitality and mental health than the norm. These outcomes were also poorer than other health outcomes.
- The trends in health outcomes of these family caregivers during the 12-month critical period of recovery of hip-fractured elders after hospital discharge indicated that role performance-related health outcomes improved significantly, but mental health and general health declined during the first year.
- Perceived availability of social support was positively related to trends in most health outcomes for these family caregivers.

Implications for practice and/or policy

- Homecare nurses need to pay specific attention to health outcomes, especially general health, vitality and mental health of caregivers of a family member after hip-fracture surgery.
- Home nursing interventions for family caregivers of hip-fractured elders should assess and improve perceived social support early after patient discharge.

caregivers' health being a more indirect outcome than caregiver burden, as caregiver health is influenced by many variables besides the patient's condition (Morimoto *et al.* 2003). For example, stroke patients' functional status was not related to caregivers' burden in Japan, but caregiver burden predicted family caregiver's health-related quality of life (Morimoto *et al.* 2003).

Although caregiver health is an important predictor of institutionalization and hospital readmission (Shyu & Lee 2002, Shyu *et al.* 2004b), little attention has been paid to the health of family caregivers of hip-fractured elders. The findings of this study have several implications for clinical practice. First, perception-related health outcomes, including

general health, vitality and mental health, for family caregivers of hip-fractured elders appeared to be poorer than the norm and poorer than other health outcomes. Second, mental health and general health appeared to decline during the first year. Third, family caregivers' health outcomes were influenced by perceived availability of social support, with emotion-related supports perceived as least available. Thus, healthcare providers should pay specific attention to these health outcomes and social support of caregivers.

A current major health policy in Taiwan is to develop sub-acute care systems and long-term care insurance (Department of Health 2010). Although home healthcare services are reimbursed by Taiwan's National Health Insurance programme (Cheng 2003), they only serve a limited number of disabled persons (Chang *et al.* 2010), and are struggling to expand their capacity to meet the current and future health needs of the Taiwanese population. The findings of this study provide a base for assessments and home nursing care interventions of patients with hip fracture following hospital discharge. Home nursing interventions should be developed early after patient discharge to assess and improve family caregivers' perceived social support, as it is a consistent predictor of their health outcomes and would prevent patients' institutionalization and hospital readmission.

Conclusions

This study explored trends in health outcomes and the role of social support for family caregivers of hip-fractured elders in a Taiwanese sample. The findings of this study suggest that nurses, especially home care nurses, need to pay specific attention to health outcomes, especially general health, vitality and mental health of family caregivers of a family member recovering after hip-fracture surgery. Home nursing interventions should also be developed early after discharge to assess and improve these family caregivers' perceived social support. To further explore this phenomenon, future studies could be conducted on a random sample of family caregivers and with collection of prefracture health outcomes. The findings of such a study could provide the basis for future interventional studies. Similar studies may help healthcare providers in other countries with Chinese populations to develop specific intervention programmes.

Funding

This work was supported by a grant (NHRI-EX92-9023PL) from the National Health Research Institute, Taiwan.

Conflict of interest

No conflict of interest has been declared by the authors.

Author contributions

YLS was responsible for the study conception and design. YLS performed the data collection. YLS, MC, JL and MT performed the data analysis. YLS, MC, JL and MT were responsible for the drafting of the manuscript. YLS, MC, JL and MT made critical revisions to the paper for important intellectual content. YLS, MC and JL provided statistical expertise. YLS obtained funding. YLS and JL supervised the study.

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