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Original Article

Gender Differences in Risk Factors for Memory Complaints in Complicated Mild Traumatic Brain Injury Patients with Glasgow Coma Scale Scores of 14 to 15

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Purpose: Post-traumatic complaints in patients with complicated mild traumatic brain injury (mTBI) might persist for years. Among them, subjective memory complaints (MCs) are widespread. However, few studies have explored the relationship between gender, MCs, and risk factors when interference variables are considered. This study investigated whether there are gender differences in risk factors of MCs in the chronic phase of patients with complicated mTBI and Glasgow Coma Scale (GCS) scores of 14-15.

Methods: Medical records were retrospectively analyzed in several teaching hospitals in southern Taiwan. Complicated mTBI was identified through computed tomography. The complicated mTBI patients participating in this study should be injured for at least one year. Data on MCs of patients in the chronic phase of complicated mTBI was collected in structured telephone interviews.

Results: A total of 403 mTBI (229 [56.82%] males) with GCS scores of 14-15 at admission and hospitalization were identified. At the time of injury, the mean age was 40.47 ± 16.71 years, and the mean follow-up was 1.93 ± 0.60 years post-injury. Of all the patients, those who had MCs consisted of 87 (37.99%) males and 76 (43.68%) females, and there were 35 (15.28%) males, and 23 (13.22%) females had memory complaints only (MCOs). Male patients with mixed types of hemorrhage (brain contusions and subarachnoid hemorrhage [SAH]) had higher odds of MCs and MCOs.

Conclusion: In male complicated mTBI patients, during the chronic phase, those with brain contusions and SAH may have higher risks with MCs and MCOs. These findings might provide meaningful information for clinical workers on healthcare

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planning in the future.

Keywords: contusions, gender differences, memory complaints, subarachnoid hemorrhage, traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) is being recognized as a chronic disease process rather than an event (1). The majority of TBI is classified as mild TBI (mTBI) (2, 3), which is frequently referred to as a "silent epidemic" because its functional outcomes are usually invisible (3). However, it is clear that the consequences of mTBI are often not as mild as expected (4) and that further research about the prediction of the functional outcome is needed (5).

It is common in clinical practice to see mTBI patients complaining about residual problems after TBI, and part of them will actually develop persisting post-traumatic complaints (PTC) or even strengthen over time (6). Early detection of patients at risk of persistent PTC is essential. Cicerone and colleagues (1995) suggested that PTC offers meaningful clinical information related to the nature of the disability, treatment needs, and functional outcomes. Patients with mTBI complained about how residual disabilities interfered with their returning to work or work status (7, 8). Emanuelson and colleagues (2003) revealed that the mTBI group scored significantly lower on the SF-36 health-related quality of life survey than the normative control group. They also found a significant correlation between the frequency of complaints and the score on the quality of life. The more often they make complaints, the lower their score is on the quality of life.

Nevertheless, prior efforts to identify PTC relied on surveying the entire constellation rather than analyzing individual symptoms, which likely reflects different etiological pathways (9, 10). Besides, there were different opinions regarding the related factors of PTC; one is neurological factors, such as neurological sequelae of the mTBI, another is psychological factors, such as premorbid psychiatric disorders. Some researchers view PTC as the phenomenon of complex interactions among pre-injury, neurological and psychosocial factors (11). The controversial opinions were the cause of many researchers attempting to determine the causes of PTC. Several studies have shown gender differences in PTC after mTBI. Females reported significantly more complaints (12), which might be related to psychosocial factors (13). Gender is a complex but critical pre-injury factor in healthcare planning after TBI because individuals might face various experiences and gender characteristics20 and have differences in high vulnerability based on their pathology (12, 14, 15). Therefore, viewing patients in terms of gender might be a step toward more personalized care (15).

Complaints about memory, forgetfulness or difficulty remembering were the most common cognitive problems reported in mTBI patients (16-18). Dikmen and colleagues (2010) stated significant differences only in memory complaints between the TBI severity subgroups. Su and colleagues (2017) found that mTBI patients who were unstably employed six months after injury reported more memory or emotional complaints without muscle power or response speed (MEMR) complaints compared to patients who were stably employed. However, the possible difficulties in interpreting memory complaints and uncovering the potential recovery pattern were caused by multiple potential confounding factors (16). Previous history of brain injury, prior neurological diseases, preexisting psychiatric problems (16-18), lower intelligence (19) co-occurrence of post-traumatic stress disorder (PTSD) symptoms (16, 20-22), and other self-reported cognitive or emotional problems (21) might cause mTBI patients to perceive memory difficulties and become more prone to experience such difficulties than those without. In addition, mTBI is a heterogeneous diagnosis with a wide range of possible clinical outcomes (23, 24) that have complicated dependencies on the combination of pre-injury and severity of brain injury factors. When an mTBI patient undergoes computed tomography (CT) evidence of visible skull fracture or intracranial abnormalities, they are defined as complicated mTBI (25). Patients with

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complicated mTBI have poorer long-term post-injury prognoses in comparison with uncomplicated mTBI (26, 27), and they might continue to report MCs for up to 24 months after the injury (7, 17, 28). Evidence of brain contusions on CT scans is an important risk factor of poor functional outcome according to the Glasgow Outcome Scale (GOS)(28) and complaints (7, 21). The Glasgow Coma Scale (GCS) is frequently used to classify the severity of brain injuries, and a TBI with a GCS score of 13 is considered mild or moderate. Mena and colleagues (2011) suggested that classifying an admission GCS score of 13 as moderate TBI yields a more accurate prognosis at discharge.

Taking the above findings together, we found that the debate remains on the related factors of PTC persist in some mTBI patients. Furthermore, long-term evaluations of gender-specific outcomes, after complicated mTBI had been less conducted, we attempted to understand gender differences better. We aimed to investigate the frequency of memory complaints among male and female patients after excluding the confounders and explore gender differences in risk factors for memory complaints observed in the chronic phase of complicated mTBI patients with GCS scores of 14 to 15.

2. Methods

2.1. Participants and procedures

We screened 1671 patients with complicated mTBI and GCS scores of 14 to 15, all of whom were admitted to teaching hospitals in southern Taiwan from 2011 to 2014. Human Experiment and Ethics Committee approved all procedures. Complicated mTBI patients were classified based on their CT evidence of visible skull fracture or intracranial abnormalities, including epidural hemorrhage (EDH), subdural hematoma (SDH), subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and brain contusions (26). The chronic phase was defined as up to one year after the injury. To ensure that the recruited participants were eligible for the study, patients with complicated mTBI that had GCS scores lower than 13 at admission and after having been hospitalized, prior neurosurgical intervention, below 12 years old, had an intellectual disability, hearing problems, history of neurological diseases or psychiatric diseases, prior TBI, or suspected of having PTSD symptoms, were excluded.

Participants were enrolled in the study in three steps. First, the study excluded 853 patients who met one or more exclusion criteria and the remaining 818 patients were recruited. Second, during a follow-up structured telephone interview at a mean of 1.93 years after the TBI (median = 1.98 years, interquartile range [IQR] = 1.43 years to 2.31 years), there were 87 invalid telephone numbers and 311 (38.02%) patients refused to have an interview. Thus, a total of 420 patients completed the interview. Third, the 17 patients with suspected PTSD symptoms were eliminated. In the end, a total of 403 patients participated in this study.

2.2. Measures

Retrospective review of medical records

Demographic (gender, age at time of injury, and educational level) and neurological factors (injury-related data and other clinical information) of the patients were collected by our study group, which included physicians (neurosurgeon, neuroradiologist, physiatrist, and orthopedist) and clinical neuropsychologists, who reviewed the patients' medical records. The severity of the neurological damage was determined using the Common Data Elements (CDEs)- GCS score, increased intracranial pressure (IICP), injury severity score (ISS), and loss of consciousness (LOC)- established in 2011 by the National Institute of Neurological Disorders and Stroke (NINDS). Clinical signs of IICP included dizziness, headache, vomiting, and nausea. ISS is a rating of the three most severely injured body regions. If ISS scores were above 15, it would be categorized as severe. We recorded trauma-related abnormalities as radiological parameters on CT data related to EDH, SDH, SAH, ICH, and brain contusions.

Structured telephone interviews

Clinical neuropsychologists or trained researchers conducted the 10 to 15 minutes structured telephone interviews. All of the interviewers had been trained and were supervised by an experienced supervisor.

The Interview of Subjective Complaints (ISC) measured PTC, such as muscle power, response speed, memory, and emotion. It was reliable and could be done over telephone or face-to-face interviews

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Table 1. Demographic and neurological characteristics of male and female with complicated mTBI

Variables	Male N=229	Female N=174	*P* (χ^2)
Age at injury (years)			0.754
≤ 24, n (%)	62 (27.07%)	40 (20.99%)	
25-40, n (%)	58 (25.33%)	43 (24.71%)	
41-54, n (%)	55 (24.02%)	44 (25.29%)	
≥ 55, n (%)	54 (23.58%)	47 (27.01%)	
Education (years)			0.006**
0-6, n (%)	30 (13.10%)	42 (24.14%)	
7-12, n (%)	131 (57.21%)	77 (44.25%)	
> 13, n (%)	68 (29.69%)	55 (31.61%)	
Mechanism of injury			0.010*
Motor vehicle collision[a], n (%)	173 (75.55%)	154 (88.51%)	
Fall, n (%)	47 (20.52%)	18 (10.34%)	
Assault, n (%)	8 (3.49%)	2 (1.15%)	
Blunt head trauma, n (%)	1 (0.44%)	0 (0.0%)	
Isolated skull fracture			0.197
Yes, n (%)	12 (5.24%)	4 (2.30%)	
No, n (%)	217 (94.76%)	170 (97.70%)	
LOC			0.916
Yes, n (%)	137 (59.83%)	105 (60.34%)	
No, n (%)	92 (40.17%)	69 (39.66%)	
ISS ≥ 16			0.612
Yes, n (%)	44 (19.21%)	30 (17.24%)	
No, n (%)	185 (80.79%)	144 (82.76%)	
Isolated EDH			0.310
Yes, n (%)	7 (3.06%)	2 (1.15%)	
No, n (%)	222 (96.94%)	172 (98.85%)	
Isolated SDH			0.666
Yes, n (%)	22 (9.61%)	19 (10.92%)	
No, n (%)	107 (90.39%)	155 (89.08%)	
Isolated SAH			0.385
Yes, n (%)	76 (33.19%)	65 (37.36%)	
No, n (%)	153 (66.81%)	109 (62.64%)	

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Isolated ICH			0.659
Yes, n (%)	5 (2.18%)	5 (2.87%)	
No, n (%)	224 (97.82%)	169 (97.13%)	
Isolated contusions			1.000
Yes, n (%)	6 (2.62%)	5 (2.87%)	
No, n (%)	223 (97.38%)	169 (97.13%)	

LOC: loss of consciousness; ISS: injury severity score; EDH: epidural hematoma; SDH: subdural hemorrhage; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage; ISS: injury severity score. [a] Motor vehicle collision includes motor vehicle, motorcycle, and pedestrian hit by vehicle collisions.
*P < 0.05, ** P < 0.01, *** P < 0.001.

in the clinic (8). The interview began with an open-ended question intended to determine whether the patients had post-injury cognitive sequelae. The interviewers than asked questions, for example 'After your injury, did you have memory problems?'. If the answer was "yes," it would be recorded as cognitive complaints, such as memory complaints (MCs). The reliability and correlation validity of 133 patients with TBI showed that the Cronbach alpha of four questions was 0.668. There was significant correlation of emotion complaint with several subscale of the 50-item Brief Symptom Rating Scale (BSRS-50)(29), including total scale ($p<0.0001$), anxiety ($p<0.01$), depression ($p<0.01$), hostility ($p<0.01$), obsessive ($p<0.01$), additional symptoms ($p<0.01$), interpersonal hypersensitivity ($p<0.01$), psychiatric symptoms ($p<0.01$). The memory complaints correlated with additional symptoms ($p=0.02$) and hostility ($p=0.043$). Participants who reported MCs without any other complaints were classified as having memory complaints only (MCOs).

The startle, Physiological Arousal, Anger, and Numbness–Chinese version (SPAN-C) consists of four items and is used to screen PTSD symptoms in patients with TBI (30-32). It is the 5 points assessment from the patients'' perspective (0 = Not at all, 1 = A little, 2 = Moderately, 3 = Very much, 4 = Extremely). For example, one question is: 'Have you become easily frightened in the past week?' When the cut-off point is 5, it has 78% diagnostic accuracy, 78% sensitivity, and 77% specificity.

2.3. Statistical Analysis

Categorical variables were analyzed with the chi-square (χ^2). Fisher's exact test was used when the expected frequency for any cell was smaller than 5. Odds ratio (OR) was used to measure the strength of the association between variables. According to the publication of Chen, Cohen, & Chen (2010), the values of OR were 1.68, 3.47, and 6.71, which refer small, medium, and large associations between variables respectively. All statistical analyses were done using SPSS 17.0 for Windows, and *P*-value lower than 0.05 was considered statistically significant.

3. Results

3.1. Demographic and neurological characteristics

Of the 403 complicated mTBI patients, the mean age was 40.47 ± 16.71 years old. Their medical records showed that 116 (28.78%) patients had a GCS of 14 in the emergency room (ER).

There were 229 (56.82%) male patients and 174 (43.18%) female patients. Chi-square analyses revealed significant difference between gender on demographic characteristics, including the years of education and mechanism of injury. Neurological characteristics were comparable between males and females (Table 1).

3.2. Subjective MCs and MCOs

Among the 403 participants, 163 (40.45%) patients complained about MCs, and 58 (14.39%) complained about MCOs.

Of the 229 male patients, there were 87 (37.99%) complained about MCs and 35 (15.28%) complained about MCOs, respectively. Of the 174 female patients, there were 76 (43.68%) complained about MCs, and 23 (13.22%) complained about MCOs.

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Table 2. Memory complaints ratios of patients with complicated mTBI

Type of complaints	Male N=229	Female N=174	P (χ^2)
MCs	87 (37.99%)	76 (43.68%)	0.249
MCOs	35 (15.28%)	23 (13.22%)	0.558

MCs: memory complaints; MCCs: memory complaints combined; MCOs: memory complaints only.

there were no significant differences between males and females in MCs and MCOs (Table 2).

3.3. Risk factors of MCs and MCOs

Male patients with mixed types of hemorrhage, brain contusions and SAH, were statistically associated with complaints MCs (χ^2 = 7.098, OR = 2.83, 95% CI: 1.29-6.21) and MCOs (χ^2 = 8.686, OR = 3.48, 95% CI: 1.46-8.28). However, these relationships were not found among female patients. (Table 3 and 4).

4. Discussion

This study found that MCs and MCOs were frequently reported by female and male patients with complicated mTBI and GCS scores of 14 to15. We confirmed the findings of the previous studies (7, 17, 28), which reported that MCs persisted after complicated mTBI. Regarding gender differences, no gender differences were found in MCs after mTBI in some studies (33, 34); another study supports those females at higher risk of MCs (17). It might suggest that mTBI and complicated mTBI have different patterns in PTC in the chronic stage. In addition, clinical practice and research findings suggest that the appearance of MCs is often related to the patient's history of physical and psychiatric problems, concurrent emotional state, or other complaints (16, 17, 20-23, 35). Those patients with a history of neurological diseases or psychiatric diseases or suspected of having PTSD symptoms were excluded to control the factors that might confound MCs to

Table 3. Risk factors of memory complaints (MCs)

Risk factors	Male (n = 87)	χ^2	*P*	OR (95% CI)	Female (n = 76)	χ^2	*P*	OR (95% CI)
LOC	56 (40.9%)	1.205	0.272	1.36 (0.79-2.36)	51 (48.6%)	2.577	0.108	1.66 (0.89-3.10)
ISS ≥ 16	22 (50.0%)	3.334	0.068	1.85 (0.95-3.59)	12 (40.0%)	0.199	0.655	0.83 (0.37-1.86)
Isolated EDH	3 (42.9%)	0.073	1.000	1.23 (0.27-5.64)	1 (50.0%)	0.033	1.000	1.29 (0.80-21.02)
Isolated SDH	7 (31.8%)	0.394	0.530	0.74 (0.29-1.90)	9 (47.4%)	0.118	0.731	1.18 (0.46-3.07)
Isolated SAH	24 (31.6%)	1.985	0.159	0.66 (0.37-1.18)	28 (43.1%)	0.015	0.902	0.96 (0.52-1.79)
Isolated ICH	3 (60.0%)	1.051	0.371	2.50 (0.41-15.27)	0 (0.00%)	4.819	0.069	0.55 (0.48-0.63)
Isolated contusion	3 (50.0%)	0.377	0.676	1.66 (0.33-8.39)	2 (40.0%)	0.028	1.000	0.86 (0.14-5.26)
Contusion skull fracture	11 (52.4%)	2.032	0.154	1.91 (0.78-4.71)	5 (83.3%)	3.97	0.087	6.83 (0.78-59.75)
Contusion EDH	1 (16.7%)	1.189	0.275	0.32 (0.04-2.77)	0 (0.0%)	0.780	1.000	0.56 (0.49-0.64)
Contusion SDH	9 (40.9%)	0.088	0.767	1.15 (0.47-2.80)	7 (46.7%)	0.060	0.807	1.14 (0.40-3.30)
Contusion ICH	3 (33.3%)	0.086	1.000	0.81 (1.20-3.32)	1 (20.0%)	1.173	0.388	0.31 (0.03-2.86)
Contusion SAH	18 (60.0%)	7.098	0.008**	2.83 (1.29-6.21)	9 (52.9%)	0.657	0.418	1.51 (0.55-4.12)

MCs: memory complaints; MCOs: memory complaints only; OR: odds ratio; CI: confidence interval; GCS: admission Glasgow coma score; LOC: loss of consciousness; ISS: injury severity score; EDH: epidural hematoma; SDH: subdural hemorrhage; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage. *P < 0.05, ** P < 0.01, *** P < 0.001.

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uncover a pattern of recovery after mTBI in the chronic phase and provide supporting evidence for precision medicine. Although we considered the confounding factors in this study, memory complaints were also correlated with brain pathology. The current study's findings indicate that MCs and MCOs might contain meaningful information rather than mere noise.

This study extends the findings of previous studies by showing the mixed types of brain contusions and SAH were the risk factors of MCs and MCOs in the chronic phase of complicated mTBI male patients, even if the GCS score was only 14 to15. Limited evidence suggests that the response of male and female brains to traumatic injury differed, and that males are more vulnerable than females (36, 37). The finding of this study might point out that brain pathology has implications that reflect the need for ongoing health service and a different rehabilitation program for male complicated mTBI patients. Although both neurological and psychosocial factors might affect gender differences and shape health behaviors and functional outcomes post-TBI (14), only the neurological risk factors of males were released. Relatively, the risk factors for female patients remain unknown in this study, and that further research is needed to clarify this issue.

The frontal and temporal lobes are often the most frequent sites of brain contusions (38). The frontal (39, 40) and temporal (40, 41) regions are exclusively engaged during the process of gaining access to stored memories. Therefore, it seems reasonable that patients with brain contusions would have more MCs than patients without. Iaccarino et al. (2014) found that clinical features and outcomes of brain contusions are heterogeneous. Thus, the most reasonable indicator is a combination of clinical data (42). Our findings suggest that mixed types of hemorrhage on radiological parameters are a better predictor of outcome than hemorrhage alone; this can shed light on the fundamental mechanisms underpinning PTC response and how different brain injury pathology

Table 4. Risk factors of memory complaints only (MCOs)

	Male (n = 35)	X^2	*P*	OR (95% CI)	Female (n = 23)	X^2	*P*	OR (95% CI)
LOC	22 (16.1%)	0.158	0.691	1.16 (0.55-2.44)	12 (11.4%)	0.739	0.390	0.68 (0.28-1.64)
ISS ≥ 16	10 (22.7%)	2.331	0.127	1.88 (0.83-4.28)	4 (13.3%)	0.000	1.000	1.01 (0.32-3.22)
Isolated EDH	2 (28.6%)	0.985	0.291	2.29 (0.43-12.30)	0 (0.0%)	0.308	1.000	0.87 (0.82-0.92)
Isolated SDH	3 (13.6%)	0.051	0.821	0.86 (0.24-3.09)	2 (10.5%)	0.135	1.000	0.75 (0.16-3.49)
Isolated SAH	8 (10.5%)	1.988	0.158	0.55 (0.24-1.28)	7 (10.8%)	0.543	0.461	0.70 (0.27-1.81)
Isolated ICH	1 (20.0%)	0.088	0.567	1.40 (0.15-12.88)	0 (0.00%)	0.784	1.000	0.86 (0.81-0.92)
Isolated contusion	1 (16.7%)	0.009	1.000	1.11 (0.13-9.81)	1 (20.0%)	0.206	0.512	1.67 (0.18-15.64)
Contusion skull fracture	5 (23.8%)	1.298	0.255	1.85 (0.63-5.44)	2 (33.3%)	2.192	0.139	3.50 (0.60-20.31)
Contusion EDH	1 (16.7%)	0.009	1.000	1.11 (0.13-9.81)	0 (0.0%)	0.153	1.000	0.87 (0.82-0.92)
Contusion SDH	6 (27.3%)	2.70	0.100	2.30 (0.83-6.36)	2 (13.3%)	0.000	1.000	1.01 (0.21-4.80)
Contusion ICH	2 (22.2%)	0.348	0.630	1.62 (0.32-8.14)	1 (20.0%)	0.206	0.512	1.67 (0.18-15.64)
Contusion SAH	10 (33.3%)	8.686	0.003**	3.48 (1.46-8.28)	4 (23.5%)	1.746	0.248	2.24 (0.66-7.56)

MCs: memory complaints; MCOs: memory complaints only; OR: odds ratio; CI: confidence interval; GCS: admission Glasgow coma score; LOC: loss of consciousness; ISS: injury severity score; EDH: epidural hematoma; SDH: subdural hemorrhage; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage.
*P < 0.05, ** P < 0.01, *** P < 0.001

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There are some limitations to this study. Firstly, although telephone interviews are convenient, practical, and often clinically useful, they might be unreliable for example, because self-reports can be influenced by the order of the questions. Since a structured questionnaire was used, questions were asked in the same sequence. If the counterbalance of a structured interview is a concern, this would be this study's limitation. Secondly, this study cannot identify the correlation between objective functions and PTC, a concern that shall be discussed in future research. Third, subtle trauma-related abnormalities in complicated mTBI may only be visible using advanced neuroimaging, such as white matter microstructure (43), which can offer more information in PTC and further healthcare planning. Since mTBI makes up most of TBI, exploration and establishment of more delicate imaging risk factors are needed.

5. Conclusions

It is essential to recognize and study gender differences because this might lead to the future development of separate healthcare planning and strategies for different gender. Brain contusions and SAH in patients with complicated mTBI might be markers for detecting high-risk male patients with MCs and MCOs in the chronic phase. Such findings might point to valuable opportunities for prevention and provide meaningful information for healthcare planning, tailored rehabilitation program, and disease adaptation following complicated mTBI to minimize ongoing sequelae.

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