Factors Influencing the Improvement of Activities of Daily Living During Inpatient Rehabilitation in Newly Diagnosed Patients with Glioblastoma

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Abstract

Purpose

To identify pre-, intra-, and postoperative factors influencing the improvement of the activities of daily living (ADL) in newly diagnosed patients with glioblastoma (GBM), we investigated the characteristics and variable factors and overall survival.

Methods

A total of 105 patients with GBM were retrospectively analyzed and categorized into three groups according to the quartile of change of Barthel index score from admission to discharge: deterioration (n = 25), no remarkable change (n = 55), and good recovery (n = 25). We compared with the characteristics, variable factors, and overall survival of patients with deterioration and good recovery after tumor resection.

Results

There was statistically different in the pre-, intra-, and post-operative factors between the groups. Multiple regression analysis identified four significant predictor variables that may influence the improvement of ADL after surgery: the improvement of motor paralysis after surgery, mild fatigue during chemoradiotherapy, poor Karnofsky performance status at admission, and length up to early walking training onset. The median overall survival was significantly different between the patients with deterioration (10.6 months, 95% CIs, 5.19–16.00) and good recovery (18.9 months, 95% CIs, 8.61–29.18) (p = 0.025).

Conclusion

This study identified four factors influencing the improvement of ADL after surgery. In addition, a structured inpatient rehabilitation programs can be performed safely and improve functional outcomes, which may contribute to the survival prognosis.

Introduction

Glioblastoma (GBM) is the most common and aggressive brain tumor, with a median age of 65 years at diagnosis [1], and is reportedly diagnosed in 12% of all brain tumor patients [2]. The initial treatment consists of a safe surgical resection followed by concurrent radiotherapy and temozolomide (TMZ) followed by another 6 months of adjuvant TMZ [3]. Therapeutic advances in oncology have prolonged the survival of individuals with brain tumors even if these individuals are often left with residual neurological deficits and psychological impairments [4]. However, patients with GBM suffer from long-

term physical and psychological impairments that limit their daily activities and participation because of factors related to the tumor or the treatment they receive [5-7].

Some studies have demonstrated that the prognostic factors that are important for survival in patients with GBM are the age at surgery, the location of tumor, multifocal or bilateral tumor, and the extent of resection [8, 9]. The prognostic factor of functional outcome has been studied in patients with brain tumors using the performance status (PS), which is considered a functional assessment tool [10, 11]. Notably, the patient' performance and function are usually assessed using the Karnofsky performance status (KPS) as a general assessment of patients with cancer [12]. Several studies have determined that a KPS score of 60 or 50 or less usually denotes a poor functional status in the clinical setting [11, 13]. Therefore, preoperative PS has long been recognized as major independent prognostic factor in patients with GBM [11]. However, some patients with a good preoperative PS will become functionally impaired because of perioperative complications and surgically acquired neurologic deficits [11, 14]. In contrast, some patients with poor preoperative PS show an improvement in their functional status after surgery [11]. Our anecdotal clinical experience seems to be associated with the pre-, intra-, and postoperative factors for the improvement of the patient' performance and functional status after surgery. However, few studies have investigated the pre-, intra-, and postoperative factors influencing the improvement of the functional status such as activities of daily living (ADL) in patients with GBM. Therefore, this study focused on identifying the factors influencing the improvement of the ADL in patients with GBM after tumor resection.

As patients with newly diagnosed GBM can be sources of significant functional impairments, they need rehabilitation to improve their disability after tumor resection. Several studies have demonstrated that patients with brain tumors who received inpatient rehabilitation improved their functional status during the course of the treatment [4, 5, 10, 15–17]. Exercise rehabilitation can maintain or improve the functional performance and quality of life (QOL) in patients with GBM, even during medical treatment regimens [18]. In addition, clinical research has established the efficacy of appropriate exercises in counteracting physical impairments including fatigue and functional decline, cognitive impairment, and psychological effects such as depression and anxiety in patients with brain tumors [19]. Furthermore, significant improvements in the functional status and health-related QOL during inpatient rehabilitation have been associated with longer survival after discharge [5, 10]. In contrast, Roberts et al. [17] reported that no statistical difference in the overall survival was found in GBM patients who did and did not receive inpatient rehabilitation. Therefore, whether functional recovery during inpatient rehabilitation influences the overall survival is controversial. Although the improvement of the functional outcome during inpatient rehabilitation was not associated with survival after discharge, the palliation of symptoms and improvement of the functional outcome, including ADL may be attributed to an improvement of the health-related QOL, which are important goals for the treatment of patients with GBM [20].

However, few investigations have been conducted to compare newly diagnosed patients with GBM who had aggravated or improved functional status in inpatient rehabilitation after tumor resection. To the best

of our knowledge, one study reported a comparison between inpatient rehabilitation responders and non-responders by the functional gains from admission to discharge using the functional independence measure (FIM) [17]. In our hospital, almost patients with GBM receive rehabilitation services after surgery to improve the neurological deficits or ADL such as locomotion. Therefore, we focused on the improvement of ADL from admission to discharge of patients with GBM using Barthel index (BI) scores. The BI score is correlated with the KPS of patients with brain tumors [21] and is easy to use for medical staff. In addition, it is reliable and sensitive to change and a well-validated scale of ADL, which is widely used in patients with neurological disability after stroke [22].

The present study aimed to identify the pre-, intra-, post-operative, and rehabilitation-related factors influencing the improvement of ADL from admission to discharge in newly diagnosed patients with GBM. Therefore, we investigated the characteristics, variable factors, and overall survival of patients with deterioration and good recovery after tumor resection.

Methods

Study design

This study was designed to retrospectively review the impact of the characteristics and variable factors and overall survival of patients with deterioration and good recovery of ADL from admission to discharge in newly diagnosed patients with GBM who were enrolled in the database of the Medical Record of Kagoshima University Hospital. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of Kagoshima University Graduate School of Medical and Dental Sciences.

Patients population

A total 110 patients with newly diagnosed GBM who were admitted to the neurosurgery department between January 2011 and October 2016 were analyzed in this study. All the patients underwent surgical tumor resection. Subsequently, they received rehabilitation services, including physical, occupational, and speech therapies during hospitalization for neurologic, physical, and psychological impairments. However, five patients did not receive inpatient rehabilitation after surgery. Therefore, a total of 105 patients with GBM were included in the study. First, we investigated the BI score of all patients at admission, at 7 days after surgery, and at discharge. The median BI score of all patients was 65 at admission (interquartile range [IQR]: 35 – 90), 30 at 7 days after surgery (IQR: 0 – 60), and 65 at discharge (IQR: 20 – 90). Furthermore, we calculated the change of BI score from admission (pre-operation) to discharge, and the median change of BI score was -5 (IQR: -20 – 5) (Supplementary Figure 1). Therefore, the present study was categorized into three groups by a quartile of change of BI score: the 1st quartile (≤ -25, n = 25, deterioration group), the interquartile range (n = 55, no remarkable change group). the 3rd quartile (≥ 10, n = 25, good recovery group).

Outcome measures

The patient characteristics, such as the patient's age, sex, KPS at admission, extent of resection, type of main treatment (TMZ, radiation, bevacizumab, TMZ concomitant radiation and bevacizumab), tumor location/hemisphere/size, length of hospital stay, duration from initial symptoms to surgery, initial symptoms (motor paralysis and weakness, cognitive dysfunction, headaches, visual field defect, dysphagia, and fatigue), surgery (surgery time, bleeding and transfusion volume, infusion volume, and fluid balance), adverse events during chemoradiotherapy, and duration from surgery to chemoradiotherapy were determined from the hospital's medical records. If we could not identify the data of initial symptoms in the medical records, we determined by hearing it from the patients or their families. However, the initial symptom data were missing in 5 and 3 patients in the deterioration and good recovery groups, respectively. The extent of resection was defined as gross and near total (the entire or > 95% of the enhancing tumor was resected), partial (< 95% tumor resection) and biopsy only. We excluded patients with biopsy only (deterioration group, n = 5; good recovery group, n =2) in the analysis of intraoperative factors.

With respect to the postoperative events, we defined the presence or absence of fever (≥ 38°C), infection, pneumonia, intracerebral hemorrhage, and motor paralysis of the lower limb that occurred within 7 days after surgery. Furthermore, the rate of interruption and discontinuation of chemoradiotherapy was examined as a postoperative event. The Brunstrom recovery stage (BRS) of the lower limbs is used to assess motor paralysis [23]. The deterioration of motor paralysis after the surgery was defined as a decrease of ≥ 2 stages. The presence of postoperative events and motor paralysis was assessed by rehabilitation medical doctors and physical or occupational therapists.

In addition, we examined rehabilitation-rerated factors (length up to rehabilitation onset after surgery, length up to sitting and walking training onset, change of motor paralysis, severe cognitive disorder or depression, and patients who discontinued rehabilitation).

The severity of the adverse effects was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (grade 0: no adverse event, grade 1: mild, grade 2: moderate, grade 3: sever or medical intervention is needed, grade 4: life-threatening, grade 5: death). Hematology and other adverse events, including the cognitive function, constipation, and fatigue were assessed more than once per week during chemoradiotherapy. Severe cognitive impairment and depressive symptoms were defined as depression grade 1 or higher and severe cognitive impairment as grade 3 or higher.

Furthermore, we followed the overall survival of patients with GBM. Overall survival was defined as the period from the time of surgery to the date of death or the date of the last follow-up for patients who were still alive. The overall survival time was calculated in months for all the patients.

Treatment and inpatient rehabilitation

Standard radiation therapy was started within 2 weeks after tumor resection, and concomitant chemotherapy (TMZ) was started on the first day of radiotherapy. Subsequently, adjuvant TMZ was started 4 weeks after the end of radiotherapy and was delivered for a period of 5 days every 28 days. The

rehabilitation intervention was performed for 40 minutes to 1 h a day for 5 days a week to improve the functional impairment. Rehabilitation programs were provided by means of sitting, standing and walking training as early as possible after resection based on the current trend of postoperative early mobilization in the ICU [24, 25].

Statistical analysis

Statistical analyses were performed using both parametric and non-parametric tests after the Shapiro-Wilk test. Subsequently, the three groups were compared using either a one-way analysis of variance (ANOVA) or Kruskal-Wallis test, followed by Bonferroni's post hoc tests for multiple comparisons. A one-way ANOVA was used to analyze the age, tumor size, and length of hospital stay. The Kruskal-Wallis test was used to examine the KPS at admission and BI score. Comparisons between patients with deterioration and good recovery groups were performed using Student's t-test or Mann-Whitney U test. The student's t-test was used to analyze the length from the initial symptoms to surgery, surgery time, bleeding volume, transfusion volume, infusion volume, fluid balance, length from surgery to chemoradiotherapy, length up to rehabilitation onset, length up to sitting, and walking training onset. The Friedman's test was used to examine the BI score and motor paralysis at admission, after surgery, and discharge followed by Bonferroni's post hoc tests for multiple comparisons. The chi-square test or Fisher's exact test was used for categorical variables. Cohen's effect size was used to evaluate intergroup differences [26]. Stepwise multiple regression analysis was employed to determine the predictor variable associated with the improvement of ADL from admission to discharge. The independent variables were adjusted for predictor variable (age, extent of resection, length from initial symptoms to surgery, KPS at admission), intraoperative factors (fluid balance), postoperative factors (change in motor paralysis after surgery, fever, and fatigue), and the rehabilitation factors (length up to walking training initiation). The selection of these independent predictor variable was based on previous reports or the factors that were observed to be statistically different between the deterioration and good recovery groups. As the data of 16 patients were missing, the data of a total of 89 patients were used for a stepwise multiple regression analysis. The Kaplan-Meier overall survival time distributions were compared between patients in the deterioration and good recovery groups using the log-rank test. The follow-up of the overall survival of 6 patients (deterioration group; n = 3, no remarkable change group; n =3) was not possible. Therefore, the overall survival values of the 98 patients were analyzed. The 95% confidence intervals (CIs) and corresponding p values were provided. The statistical significance was set at $p < 0.05$, and data are expressed as mean ± standard deviation (SD). Statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY, USA).

Results

Patients characteristics

The clinical and tumor characteristics of the patients are shown in Table 1. The median KPS at admission in all patients was 70 or less, and the KPS was significantly different between the three

groups, suggesting that the subjects of this study were patients with a poor performance status before the surgery. Notably, the KPS at admission of the good recovery group was significantly decreased compared with that of no remarkable change and the deterioration groups ($p < 0.05$).

Change of ADL level in deterioration and good recovery groups

In the deterioration group, the mean BI score at admission (72.2 ± 23.8) was significantly decreased after surgery (18.4 ± 22.7) and at discharge (30.6 ± 26.2, $p < 0.01$, Supplementary Figure 2). In contrast, in the good recovery group, the mean BI score at admission (44.2 ± 25.0) was not significantly decreased after surgery (42.2 ± 25.0). The mean BI score was significantly improved at discharge (79.4 ± 19.3) compared with that at admission and after surgery ($p < 0.01$).

Comparison of the deterioration and good recovery groups in the pre-, intra-, post-operative factors.

The pre-, intra-, and post-operative factors in both groups during inpatient rehabilitation are shown in Table 2. The preoperative factors showed that the length from the initial symptoms to surgery was significantly longer in the good recovery group than in the deterioration group ($p < 0.01$), and it had a large intergroup effect size.

In the intraoperative factors, the fluid balance in the deterioration group was significantly increased compared to that in the good recovery group, and had a moderate intergroup effect size.

In the postoperative factors, motor paralysis after surgery was significantly worse in the deterioration group (36%) than in the good recovery group (4%, $p < 0.01$), which had a median intergroup effect size.

Comparison of the deterioration and good recovery groups in the rehabilitation-related factors.

The rehabilitation-related factors for both groups are presented in Table 3. The motor paralysis at discharge was significantly worse in the deterioration group than in the good recovery group ($p < 0.01$), which had a median intergroup effect size. The number of patients who had no motor paralysis at discharge was significantly larger in the good recovery group than in the deterioration group ($p < 0.05$). In addition, the severe cognitive disorder or depression were significantly different between the deterioration and good recovery groups ($p < 0.01$); additionally, these factors had a high intergroup effect size.

Adverse event during chemoradiotherapy

The adverse events were classified as hematologic or treatment-related non-hematologic events (Table 4). In the hematologic toxicities, the majority of the patients were grade 0 or less than grade 2 in both groups. In the non-hematologic toxicities, grade 1 or 2 fatigue and fever were more frequently observed in the deterioration group than in the good recovery group. There was a significant difference in the fatigue and fever between the groups ($p < 0.01$).

Factors influencing improvement of ADL and overall survival

The stepwise multiple regression analysis revealed four significant predictor variables: the change of motor paralysis after surgery, fatigue during chemoradiotherapy, KPS score at admission, and the length up to walking training onset after surgery (Table 5).

The median overall survival for the entire cohort was 13.6 months (95% CI, 10.52–16.66). The median overall survival of the patients in deterioration group was 10.6 months (95% CI, 5.19–16.00) and those of the patients in the good recovery group was 18.9 months (95% CI, 8.61–29.18). The median overall survival was significantly longer the good recovery group than in the deterioration group (Figure 1, p = 0.025).

Discussion

Significant gains due to inpatient rehabilitation are observed in areas of mobility such as transfer or locomotion and self-care [17]. Our results suggest that the presence of motor paralysis greatly contributes to the improvement of ADL in patients with GBM. Motor deficits are one of the most important factors affecting the ability to perform ADL in stroke patients [27]. Therefore, the presence of motor paralysis and muscle weakness as the initial symptoms was observed to directly lead to ADL disorders and may require early surgical treatment. Notably, the improvement of motor paralysis after surgery may be the most important factor that influenced the gain of functional status of patients with GBM from admission to discharge.

Furthermore, our results suggest that mild fatigue during chemoradiotherapy may contribute to the improvement of the functional status of patients with GBM. Fatigue is a common and severe symptom in patients with tumors, which often influences outcomes such as the functional status [28]; additionally, severe fatigue correlates with poor physical function and QOL [29]. Chemotherapy-related fatigue peaks on the day after chemotherapy, whereas radiation therapy-related fatigue gradually accumulates over the course of the treatment [30]. However, aerobic exercise has shown consistent effects in alleviating cancer-related fatigue [29]. Furthermore, walking is an appropriate exercise for physical and mental disorders such as disuse atrophy, depression, and anxiety. The present study suggest that the intervention of early walking training is important not only for the palliation of chemoradiotherapy-related fatigue but also for improving the functional or mental status. However, it is difficult for some older patients to perform monotonous walking training owing to fatigue and mental stress by chemoradiotherapy. Further studies are needed to investigate the effects of early walking training during inpatient rehabilitation.

The preoperative KPS is one of the factors to positively influence the overall survival[11]. This study focused on the change of the ADL from admission to discharge. Therefore, our analyses indicated that poor preoperative KPS may contribute to the improvement of the ADL. The present study suggested that rehabilitation intervention after surgery can be performed safely without severe adverse and structured inpatient rehabilitation may be an important strategy to enhance the functional outcome of patients with GBM in addition to standard therapy.

The factors that positively influence the overall survival except preoperative KPS are the age at surgery, tumor location, and extent of resection [9, 11, 31]. These tumor characteristics may be associated with the onset of postoperative motor paralysis and functional status. Gliomas extending into the insular or deep area are intricately related to functionally important structures such as the motor fibers of the corona radiata and the internal capsule [32]. In addition, multifocal or bilateral tumors are important factors for survival in patients with GBM [9]. Therefore, tumor characteristics, including the tumor location and hemisphere, may be associated with the improvement of functional status. Further studies are needed to investigate the factors that influence the improvement of functional status during inpatient rehabilitation.

Regarding intraoperative factors, this study found that fluid balance was higher in the deterioration group than in the good recovery group. Early negative fluid balance is associated with lower postoperative mortality in clinically ill patients following cardiovascular surgery [33]. Similarly, our results suggest that fluid balance may contribute to postoperative mortality and in clinically ill patients following brain tumor resection. Therefore, the disorder of fluid balance might influence the functional status of patients with GBM after surgery.

Despite surgical resection and radiation therapy with or without adjuvant TMZ, the median overall survival of patients with GBM is less than 15 months [34]. A recent retrospective study reported that the 12-months -and 3 years survival rates are 40% and 10%, respectively [35]. Our results suggest that the overall survival of patients with GBM may be affected by improvements in the functional status, including ADL ability, during inpatient rehabilitation. Several studies have demonstrated that the overall survival may be extended if rehabilitation intervention improves the physical function of patients with stroke and brain tumors [5, 36].

There are a few limitations with respect to our single-hospital study. First, this was a retrospective study with a relatively small sample size in both groups. Second, the QOL is the most important outcome in patients treated for GBM. Recently, the QOL has increasingly come to focus as a key outcome parameter in patients with brain tumors [37]. Therefore, further studies are needed to investigate the association between the functional outcomes and QOL in patients with GBM. Third, this study focused on the gain of ADL in patients with GBM. Our subjects differed in the preoperative functional status between the groups, which may have affected the gain of functional outcome.

Conclusion

The present study suggests that the improvement of motor paralysis after surgery, mild fatigue during chemoradiotherapy, poor KPS at admission, and length up to early walking training onset after surgery contributed to the improvement of the ADL from admission to discharge. Although patients with GBM show poor functional status at admission, a structured inpatient rehabilitation program can be performed safely and improve functional outcomes, which may contribute to the survival prognosis.

Abbreviations

glioblastoma (GBM), activities of daily living (ADL), temozolomide (TMZ), performance status (PS), Karnofsky performance status (KPS), quality of life (QOL), functional independence measure (FIM), Barthel index (BI), Common Terminology Criteria for Adverse Events (CTCAE), Brunstrom recovery stage (BRS)

Declarations

Funding:

The authors did not receive support from any organization for the submitted work.

Conflict of interest

The authors report no conflicts of interest in this work.

Availability of data and material (data transparency)

Available from the corresponding author upon reasonable request.

Code availability Not applicable

Authors' contributions

All authors contributed to this study. This study is based on the original ideas of KN, HS. KK, AY. HY, KY, and MS performed the review and editing. SA performed the obtained data and editing graphic. KN and SH performed the literature review and wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval:

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of Kagoshima University Graduate School of Medical and Dental Sciences (No. 28-70).

Consent to participate: Not applicable

Consent for publication: Not applicable

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Tables

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Figures

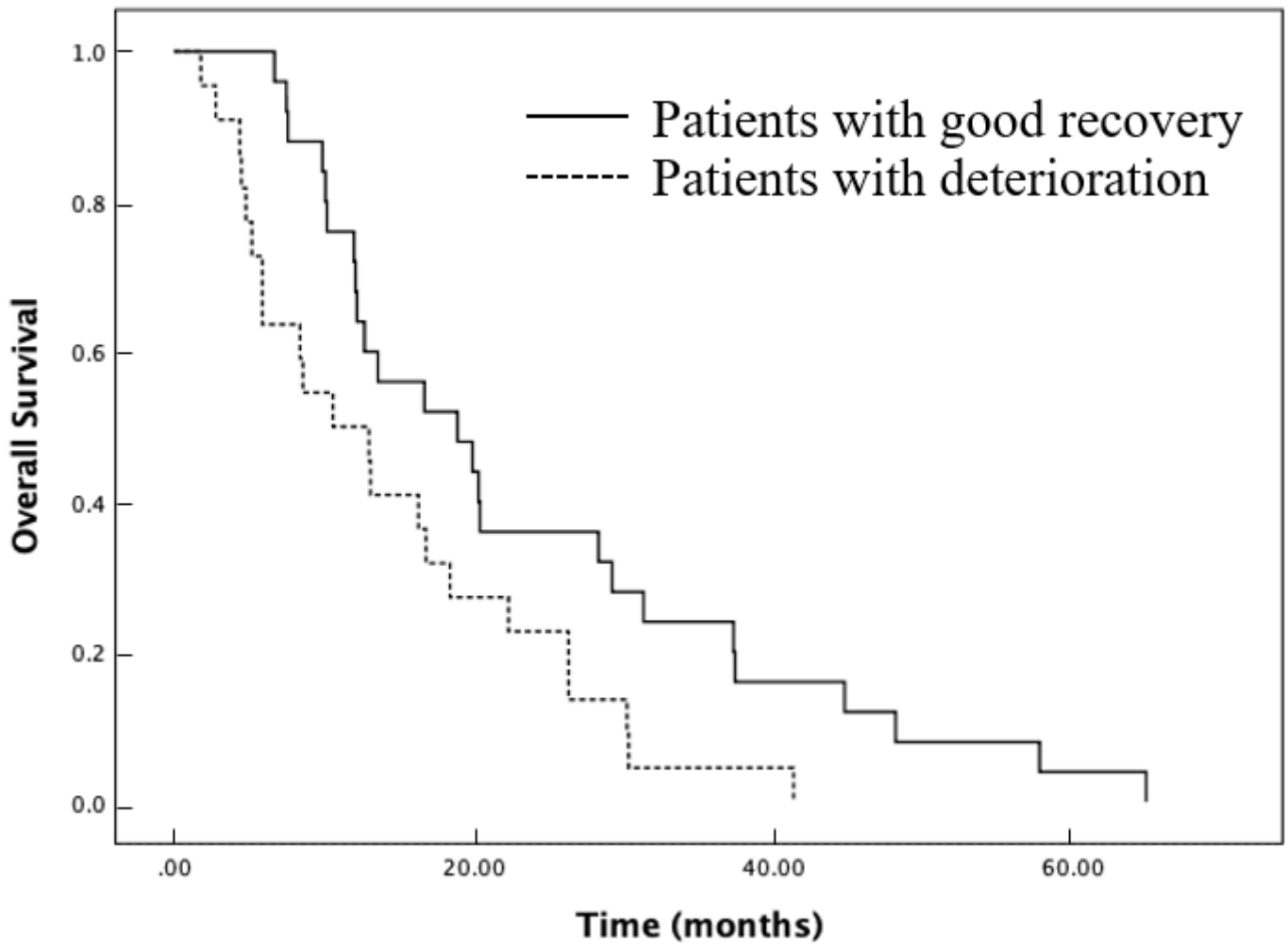

Figure 1

Kaplan-Meier estimates for mobility deterioration group (dotted line) and good recovery group (solid line).

Supplementary Files

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