Aus dem Institut/der Klinik für Thoraxchirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Zur Bedeutung der roboterunterstützten Thymektomie bei Myasthenia gravis mit okulärem Symptombeginn

The importance of robot-assisted thymectomy in selected myasthenia gravis patients with purely ocular symptoms at onset

zur Erlangung des akademischen Grades
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Contents

Abstract German
Etwa die Hälfte der Patienten weist zu Beginn einer Myasthenia gravis (MG), rein augenbedingte Symptome auf, hier als okuläre Myasthenia gravis (OMG) bezeichnet, obwohl sie häufiger so definiert wird, wenn rein okuläre Symptome 2 oder 3 Jahre nach Krankheitsbeginn anhalten. Die OMG wird oft als milde Krankheit angesehen, kann aber tiefgreifend stören und das Sehvermögen beeinträchtigen. Außerdem entwickelt mehr als die Hälfte der Patienten mit OMG sekundär eine generalisierte MG (gOMG). Obwohl die robotische Thymektomie bei Patienten mit gOMG zu einer Behandlungsoption geworden ist, gilt das für Patienten mit OMG noch nicht.

Unsere Studie untersuchte den optimalen Zeitpunkt der Thymektomie in Bezug auf den Zeitpunkt der Generalisierung Retrospektiv wurden 596 Patienten mit MG nach einer robotischen Thymektomie an der Charité Berlin untersucht. Einhundertfünfundsechzig Patienten konnten eingeschlossen werden. Patienten, die vor der Generalisierung eine Thymektomie erhielten, wurden der OMG-Gruppe (n = 73) zugeordnet, während diejenigen, die nach der Generalisierung eine Thymektomie erhielten, der gOMG-Gruppe (n = 92) zugeordnet wurden. Fünfundsechzig Patienten jeder Gruppe wurden nach dem Neigungsscore abgeglichen. Die geschätzte kumulative Rate der vollständigen stabilen Remission nach fünf Jahren in der OMG-Gruppe (49,5%) war signifikant höher als in der gOMG-Gruppe (33,4%). Eine Neigungsanpassungsanalyse wurde dann für Patienten ohne Thymom vorgenommen, und die Ergebnisse nach dem Anpassen stimmten mit der Gesamtgruppenanalyse überein.

Danach entwickelte unsere Studie ein Vorhersagemodell bei Patienten mit rein okulären Symptomen zu Beginn der MG für die Wahrscheinlichkeit einer Umwandlung in eine gOMG Weibliches Geschlecht (neue Ergebnisse und noch nicht veröffentlicht), höheres Alter zu Beginn, höherer Anti-AChR-Antikörpertiter, Seropositivität für Anti-MuSK-Antikörper, das Vorhandensein von anderen Autoimmunerkrankungen und keine Medikation mit Corticosteroiden waren signifikant mit der Entwicklung einer sekundären Generalisierung assoziiert. Die Unterscheidungsfähigkeit und Kalibrierung des endgültigen Modells zeigten eine gute Vorhersagefähigkeit mit einer concordance statistic (C-Statistic) von 0,689 für die interne Validierung. Basierend auf diesen sechs Variablen wurde dann eine Gleichung erstellt, um die Wahrscheinlichkeit einer Umwandlung in eine Generalisierung genau vorherzusagen.

Bei Patienten mit rein okulären Symptomen zu Beginn der MG, führt die Thymektomie vor der Generalisierung wahrscheinlich zu einer höheren Remissionsrate als die Thymektomie nach der Generalisierung. Die

vorgeschlagene Gleichung könnte die Wahrscheinlichkeit einer Umwandlung in eine Generalisierung vorhersagen. Eine Thymektomie sollte bei OMG-Patienten mit hohem Generalisierungsrisiko in Betracht gezogen werden, die nicht zufriedenstellend auf Kortikosteroide ansprechen oder sehr schwere Nebenwirkungen haben.

Abstract English
About half of the patients initially present with purely ocular symptoms at myasthenia gravis (MG) onset, which is here defined as ocular onset myasthenia gravis (OMG), because ocular myasthenia gravis is more frequently defined when the purely ocular symptoms last for 2 or 3 years after disease onset. OMG is often regarded as a mild disease but can be profoundly disturbing and visually disabling. Besides, more than half of the patients with OMG will develop a secondary generalized MG (gOMG). Although robot-assisted thymectomy has become a treatment option for patients with gOMG, it has not yet received much acceptance for those with OMG.

Our study aimed to explore the optimal timing of thymectomy for OMG regarding the time of generalization. We conducted a retrospective review of 596 patients with MG who underwent robot-assisted thymectomy in the Charité Berlin. One hundred and sixty-five patients were eligible for inclusion. Patients who received thymectomy before generalization were classified to OMG group (n=73), whereas those who received thymectomy after generalization were classified to gOMG group (n=92). Sixty-five patients of each group were matched according to the propensity score. The estimated cumulative rate of complete stable remission at five years in the OMG group (49.5%) was significantly higher than that in the gOMG group (33.4%). A propensity matching analysis was then performed in the nonthymomatous MG subgroup, and the results after matching were in line with the whole group analysis.

Then, we continued our work (unpublished data) to develop a prediction model in patients with purely ocular symptoms at MG onset to predict the probability of conversion to gOMG. Our results indicated that female gender, higher age at onset, higher anti-AChR antibody titer, seropositivity for anti-MuSK antibody, the presence of other autoimmune disease, and no medication with corticosteroids were significantly associated with the development of secondary generalization. The discriminative ability of the final model indicated a fair predictive ability with a concordance statistic (C-statistic) of 0.689 for internal validation. An equation was then generated based on these six variables to accurately predict the probability of conversion to generalization.

In patients with purely ocular symptoms at MG onset, thymectomy before generalization is likely to result in a higher remission rate than thymectomy after generalization does. The proposed equation might predict the probability of conversion to generalization. Thymectomy should be considered in OMG patients with a high risk of generalization who have

failed to respond satisfactorily to corticosteroids agents or have intolerable side effects from them.

Introduction

Myasthenia gravis (MG), manifested by fluctuations in severity of muscle weakness and unusual fatigue, is a rare but well-studied autoimmune disorder caused by autoantibodies directing against the acetylcholine receptors (AChRs) and other proteins at the postsynaptic membrane (1). The muscle weakness usually increases with exercise and over the course of the day, recovers after some rest with a potential of return to normal muscle strength in the morning. About half of the MG patients present with pure ocular symptoms at onset, which is defined here as having ocular onset myasthenia gravis (OMG) (2). Of these, more than half of the patients will convert to secondary generalized MG (gOMG), whereby the weakness of non-ocular muscles, e.g. bulbar and respiratory muscles and muscles of the extremities and the trunk, is developed (2).

The treatment goals for OMG are to alleviate the symptoms and prevent secondary generalization. In general, the treatment of OMG can be classified into 2 categories: symptomatic therapy and therapy targeting the autoimmune process (3). For patients with stable ptosis and who have failed to respond adequately to medical treatment, surgical ptosis repair might be helpful for some time but can become disturbing after achievement of remission, because of lagophthalmos. Prisms can be effective to correct diplopia if patients have stable and small misalignment. Cholinesterase inhibitors may improve ptosis, but not diplopia (3). Thus, many patients with OMG require immunosuppressive medications to control the symptoms, although the efficacy of immunosuppressive medications has not been proven by clinical trials either. Retrospective studies have indicated that corticosteroid agents might reduce the rate of generalization in patients with OMG (4, 5), but the well-known adverse effects make them less attractive (6). The history of thymectomy in the treatment of MG is longer than that of medical treatments, but thymectomy has not received much acceptance in the multidisciplinary treatment of OMG yet (3). The efficacy of extended thymectomy on MG was recently determined by a clinical trial about thymectomy for MG (MGTX) and its extension study, which concluded that thymectomy combined with prednisone results in better clinical outcomes in terms of improving myasthenic weakness and reducing the use of prednisone for patients with generalized MG (GMG) who are seropositive for antibody against AChR (anti-AChR antibody) and have an age at disease onset between 18 and 65 years, compared with prednisone alone(7, 8). However, some crucial questions regarding the role of extended thymectomy in several MG subgroups, including juvenile MG, elderly MG, MG seronegative for anti-AChR antibody and OMG, remain unanswered.

With worldwide scientific excellence, several approaches to thymectomy have been described and gradually modified, including transsternal, cervical, subxiphoid, video-assisted thoracic surgery and robot-assisted thymectomy, which are able to provide patients with MG excellent outcomes (20-22). In our institute, robot-assisted thymectomy has been performed for the treatment of MG, including OMG, since 2003 (20). However, in some other institutes, it seems that thymectomy stands as a treatment option for those with gOMG, but not OMG (3). Given a frequently proved time-varying effect of thymectomy for MG (13, 23), does wait-to-thymectomy until the time of generalization offer patients as good clinical outcomes as thymectomy before generalization does? The question is still pending.

On the other hand, as the prognosis varies significantly in patients with OMG, it is important to formulate an individualized treatment plan for each patient. In some patients with OMG, the ocular symptoms in particular severe ptosis and diplopia can be profoundly disturbing, thereby substantially impairing the quality of life (24). Besides, the response to treatment also differs from one patient to another, some even do not respond well to immunosuppressive agents. Given the risk of secondary generalization and long-term requirement of immunosuppressive agents, thymectomy should play a role in the treatment of these selected cases. Our previous study also indicated that in patients with purely ocular symptoms at onset thymectomy before generalization might result in a higher rate of remission than thymectomy after generalization does (25). Thus, formulating a more “aggressive” treatment plan for patients with a high risk of secondary generalization might be beneficial.

Many previous studies have aimed to identify the risk factors of secondary generalization in patients with OMG (26-28), which include: seropositivity for anti-AChR antibody, age at disease onset < 50 years, higher titer of anti-AChR antibody, female sex, history of smoking and thymic abnormalities. Moreover, a well-designed retrospective study also developed a risk score system which is comprised of three clinical variables: seropositivity of antibodies against AChRs (anti-AChR antibody), presence of comorbidity and thymic hyperplasia (29). The performance of the model is fair according to the area under the ROC curve (0.74). However, the difficulty in identifying thymic hyperplasia from the imaging findings might limit the wide use of the score system in the clinical practice.

Therefore, we aimed to compare the clinical outcomes of patients who underwent robot-assisted thymectomy before secondary generalization with that of those who underwent thymectomy afterwards. After that, we continued our work to develop a more practical model to predict the

probability of conversion to gOMG in patients with purely ocular symptoms at MG onset.

Methodology

Design of the studies

These are retrospective observational studies approved by the Ethics Committee of the Charité Berlin. The studies are performed according to the Declaration of Helsinki and its amendments. Written informed consent for the use of clinical data for retrospective analyses is not necessary according to the § 25 Landeskrankenhausgesetz Berlin.

Patients

For the published study, the inclusion criteria were confirmed diagnosis of MG with purely ocular symptoms at disease onset and underwent robot-assisted thymectomy at the Charité Berlin. Patients who underwent re-thymectomy and patients who were lost to the last follow-up were excluded. The diagnosis of MG was made by a neurologist based on the presence of clinical symptoms and a seropositivity of autoantibody test (typically anti-AChR antibody [above 0.45nM]). If tests for autoantibodies were negative, a characteristic response to acetylcholinesterase inhibitors and positive findings of neurophysiological tests were used to confirm the diagnosis (30).

In terms of the further study, patients who presented to the integrated myasthenia center in the Charité Berlin for the diagnosis or further treatment of MG with purely ocular symptoms at onset were retrospectively reviewed for inclusion. The exclusion criteria were unconfirmed diagnosis of MG, missing data regarding the secondary generalization (either the occurrence or the specific time from symptoms onset to generalization), follow-up time <= 24 months and generalized within 3 months after symptoms onset. It is worth noting that patients who did not fulfil the study criteria of MG diagnosis but later developed secondary generalization were also included in the study. The diagnosis of MG was confirmed with typical symptoms and positive findings from at least one of the following tests: seropositivity of autoantibodies (anti-AChR antibody > 0.45 nM or anti-MuSK antibody > 0.4U/ml), repetitive nerve stimulation electromyography (decrease in the amplitude >= 10%) or single-fiber electromyography (increased jitter in more than 10% of the pairs analyzed or mean jitter value > the upper limit of the normal value) and tensilon test (30).

Preoperative assessment

A computed tomography (CT) of the chest was routinely performed to screen for thymoma due to its high rate of incidence in patients with MG (31). Other preoperative assessment for MG patients included pulmonary function tests, electrocardiogram and routine blood examinations for surgery. Worthy of note were the concomitant diseases, which might

require thoughtful care from a multidisciplinary team. In our institute, the surgical contraindications were uncontrolled generalized myasthenic weakness, poor general condition and geriatric multimorbidity, such as recent myocardial infarction, severe coagulopathy and poor lung function (FEV1 <30% and/or DLCO <30%).

Surgical approach

Robotic approach to thymectomy in the Charité Berlin has been previously described in detail (20). Video documentation of the surgery has become a conventional practice. Briefly, patients with a suspected tumor were operated on through a unilateral three-trocar approach according to the anatomical location of the lesion, while patients without a suspected tumor were always operated on through the left-sided approach (Figure 1a-c). In a few cases, an additional trocar was introduced at subxiphoid to ensure the completeness of resection and the ease of specimen retrieval. In general, an en-bloc resection with the thymus, mediastinal and cervical fat and thymoma (if any) was performed for patients with MG. Typically, common locations of ectopic thymic tissue, including anterior mediastinal fat, pericardiophrenic angles, aortopulmonary window, pre-tracheal fat and lateral to phrenic nerves, were dissected free. The “no touch” surgical technique was, in principle, used if a mediastinal tumor was suspected. After a complete resection, surgical specimens were put in an Endobag and retrieved through the camera incision or the subxiphoid incision. All specimens were weighed immediately after retrieval, and then placed on the ITMIG Mediastinal Board as in situ, photographed and sent to the pathologist (Figure 1d) (32).

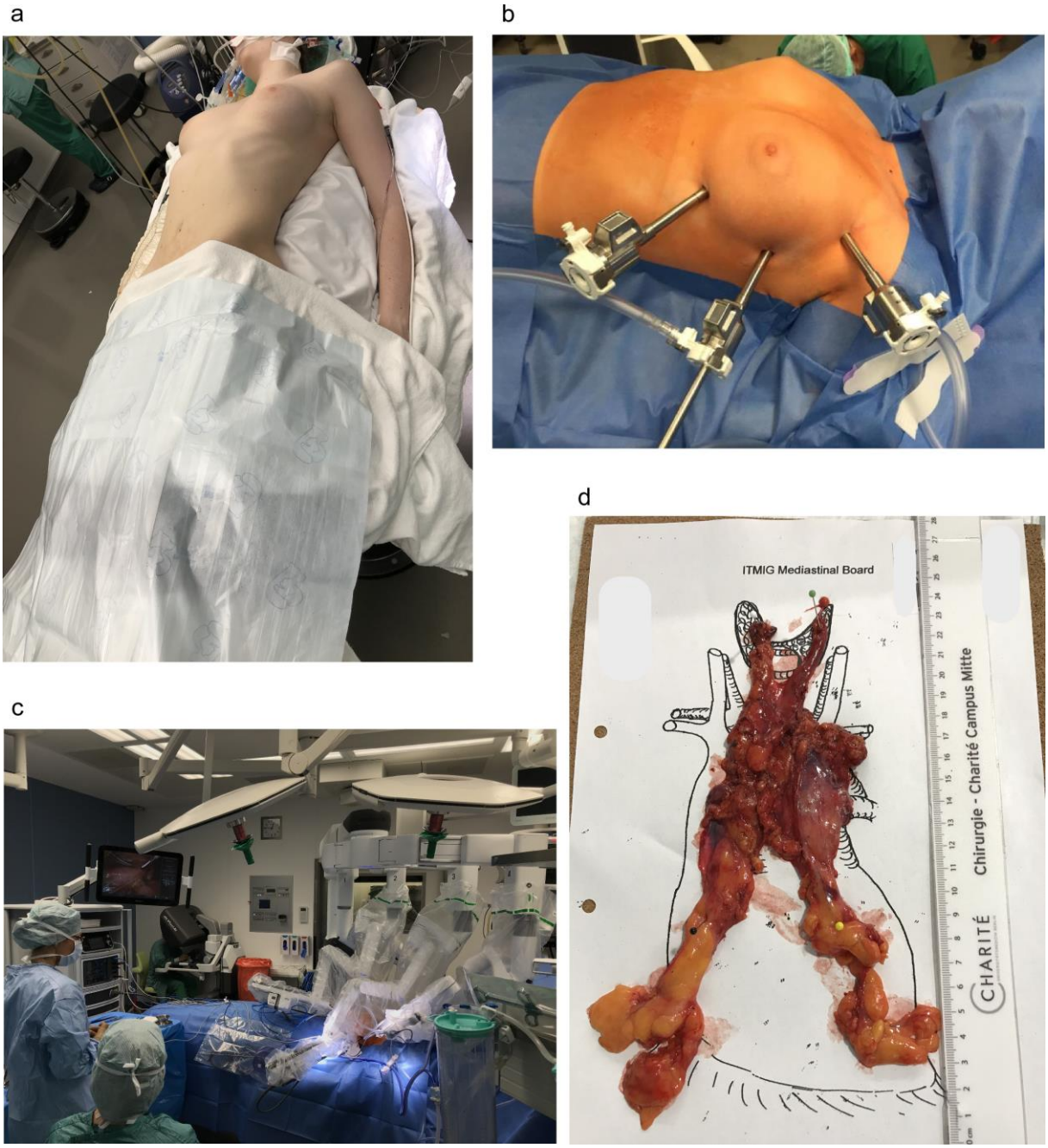

Figure 1. Robot-assisted thymectomy performed in the Charite Berlin using the da Vinci Xi surgical system. a) Patient was positioned supine to the left edge of the operating table. b) Trocars placement for left-sided approach to thymectomy. c) Operating room setup. d) Surgical specimen prepared for pathological studies.

Data collection and follow-up

For the published study, clinical variables and postoperative thymic histopathology were retrospectively extracted from the records in the hospital information system. Patients were categorized into two subgroups, OMG and generalized OMG (gOMG), according to the development of secondary generalization before surgery. The occurrence of secondary generalization was defined as the presence of non-ocular symptoms, e.g.

the weakness of arms, legs, neck, chewing, respiratory and so on, after an exclusion of the differential diagnosis. Patients usually visited neurologists, sometimes also thoracic surgeons, every 3 or 6 months for consultation, mainly medication adjustment. A telephone interview was made for a final follow-up based on a questionnaire if a patient was lost to the regular follow-up. The relatives or friends were asked about the disease course in cases when patients were unable to answer the questionnaire. The neurologic outcomes were assessed and classified according to the response to the questionnaire and the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) respectively.

Regarding the further study, baseline characteristics were extracted from a well-constructed MG database of the integrated myasthenia center. The medical records of the disease course were reviewed from the hospital information system to get more MG related information of each patient. Secondary generalization was defined as the presence of bulbar or generalized symptoms including leg weakness, arm weakness, chewing weakness, speaking problem and shortness of breath.

Statistics

For the published study, the statistical analyses were performed using R statistical software 3.5.2 (33). Categorical variables were summarized as numbers (proportions) and analyzed by Chi-Squared test, or Chi-Squared test combined with Monte Carlo method if more than 20% cells had expected frequencies less than 5. The normal distribution of continuous variables was checked and confirmed if data distribution was sufficiently symmetric on histogram and the absolute value of skewness was smaller than 0.5. Independent-samples T-test or paired Student’s t-test was used to compare normally distributed continuous variables which were summarized as means ± standard deviations (SDs); Mann-Whitney test or Wilcoxon signed-rank test was used to compare non-normally distributed continuous variables which were described as median and interquartile range (IQR).

Propensity score matching was used to reduce the selection bias between the OMG and gOMG groups. Patients with missing data, which accounted for 0.51% of all values, were excluded for matching. The propensity score, which represents for the conditional probability of undergoing thymectomy before thymectomy, was estimated using a multivariable logistic regression model. We selected variables to enter the propensity score model based on the clinical significance after a comprehensive discussion with an experienced neurologist and a statistician. The variables included gender, age at disease onset, anti-AChR antibody status, time from symptoms onset to thymectomy and thymic histopathology. The

propensity score matching was conducted using ‘matchit’ package (34). A 1:1 matching protocol without replacement was performed using the nearest neighbor method within a caliper of 0.2. Balance in the baseline covariates was assessed by the standardized difference in mean (SDM). An SDM less than 0.1 for a given covariate was considered adequate balance between the two groups, otherwise double adjustment was used to manage the imbalance. We also applied this matching analysis on a subset of patients with nonthymomatous MG.

Kaplan-Meier curves were plotted using “survival” package and log-rank test was used to compare the cumulative probability of CSR between the two groups as well as the subgroups (35). Multivariable Cox proportional hazard model was performed to explore the treatment effect after adjusting on other variables which either were not adequately balanced after matching or had a p-value smaller than 0.1 at log-rank test. A two-sided *P* value smaller than 0.05 was considered statistically significant.

As to the further study, categorical variables were described as numbers (proportions) and continuous variables were described as means ± SDs if normally distributed or medians with interquartile ranges (IQR) if not normally distributed. Variables with more than 20% of missing data were excluded, such as status of anti-titin antibody, findings of repetitive nerve stimulation electromyography and tensilon test status. Six variables were included for final analysis: gender, age at disease onset, anti-AChR antibody titer, anti-MuSK status, the presence of other autoimmune diseases (OAID) and use of corticosteroids. The earliest available value of anti-AChR antibody was documented for analysis. We did not include thymic histopathology because it is difficult, at least for some, to differentiate thymic follicular hyperplasia from normal thymus and thymic involution. Missing data were imputed by multiple imputation using “mice” package (36). Five datasets were formulated after imputation, the median values were chosen for the final analysis.

The proportionality of hazards and possible non-linear effects were tested using generalized additive models (37). Given the nonproportional hazard of age at disease onset, we chose a log-normal accelerated failure time (AFT) model to identify variables associated with the presence of secondary generalization. In AFT models, time ratios (TR) were calculated instead of hazard ratios. A TR larger than 1 means a prolongation of the survival time, whereas a TR smaller than 1 implies a shortening of the survival time. An equation was then generated based on the variables in the final model to predict the cumulative probabilities of secondary generalization at different time points. The model performance was evaluated by discrimination using the concordance statistic (C-statistic).

Results

Two hundred and forty patients underwent robot-assisted thymectomy for the treatment of MG with purely ocular symptoms at disease onset. One hundred and sixty-five patients with a female:male ratio of 1.5 were eligible for inclusion after a stepwise exclusion of 4 patients who received redo thymectomy and 71 patients who were lost to follow-up. The mean follow-up time for the whole cohort was 73.1 ± 46.03 months. Seventy-three patients were classified into OMG group (thymectomy before generalization) and 92 patients were classified into gOMG group (thymectomy after generalization) according to the timing of generalization. Figure 2 shows the flowchart of the study design. Compared to the gOMG group, time from symptoms onset to thymectomy was statistically shorter in the OMG group (10 [5-17] vs 14 [8-26] months, *P*=0.003).

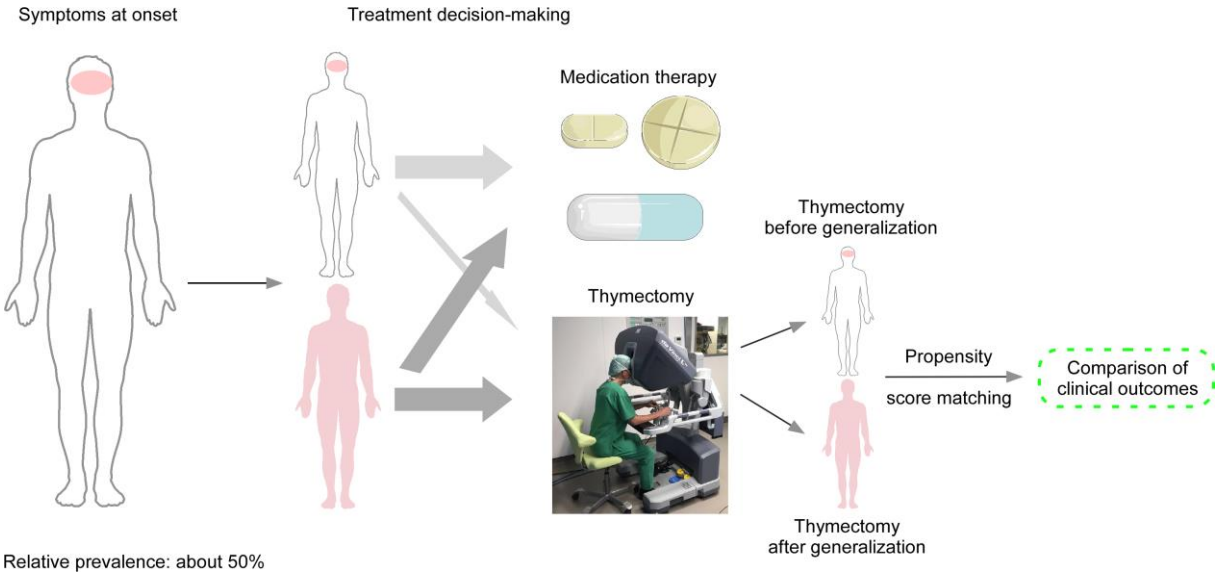

Figure 2. Flowchart of the study design. The pink color filled in the outlines represents the distribution of weakness, specifically localized ocular symptoms or generalized symptoms. The different widths of the grey arrow indicate that most patients with purely ocular symptoms receive medication therapy.

Propensity score matching was first performed in the whole cohort, 65 patients for each group were matched. There was no significant difference in all the variables between the two groups regarding the *P*-values. However, SDM for gender (0.127) showed a relatively small imbalance between the two groups. CSR was achieved in 51 (39.2%) patients in the matched cohort, 18 (27.7%) in the gOMG group and 33 (50.8%) in the OMG group. Kaplan-Meier method and log-rank test indicated that patients in the OMG group had a higher cumulative probability of CSR than those in the gOMG group did (*P*=0.0053). The 5-year estimated cumulative probabilities of CSR were 0.334 [95% confidence interval (CI) 0.176-0.462] in the gOMG group and 0.495 [95% CI 0.345-0.610] in the

OMG group. Besides, after adjustment for gender, the imbalanced variable after matching, thymectomy before generalization of OMG was still associated with the achievement of CSR [adjusted hazard ratio (HR) 2.27, 95% CI 1.27-4.1; *P*=0.006]. In addition, Kaplan-Meier analysis showed that age of 40 years or younger at disease onset (*P*=0.002) and thymic hyperplasia (*P*=0.0067) were statistically associated with achievement of CSR. In the multivariable analysis using Cox proportional hazard regression model, thymectomy before generalization of OMG (adjusted HR 2.35, 95% CI 1.32-4.19; *P*=0.004) remained significant after adjusting for age at onset and thymic histopathology.

Propensity score matching was then performed in the nonthymomatous MG cohort (n=126), a dataset of 110 patients (55 per group) was formed. Given the *P*-value for each variable, no significant difference was found between the two groups. However, SDM for anti-AChR antibody (0.172) showed a small imbalance between the two groups. CSR was obtained in 42 (38.2%) patients in the matched nonthymomatous MG cohort, 12 (21.8%) in the gOMG group and 30 (54.5%) in the OMG group. Kaplan-Meier analysis showed that patients in the OMG group had a higher cumulative probability of CSR than those in the gOMG group did (*P*=0.00041). The estimated cumulative probabilities of CSR at 5-year after thymectomy were 0.289 (95% CI 0.131-0.419) in the gOMG group and 0.535 (95% CI 0.370-0.656) in the OMG group. In addition, after adjusting for anti-AChR antibody, the imbalanced variable after matching, thymectomy before generalization of OMG was still associated with the achievement of CSR (adjusted HR 3.1, 95% CI 1.58-6.1; *P*<0.001). Similarly, Kaplan-Meier analysis also revealed that age of 40 years or younger at disease onset (*P*=0.017), thymectomy within 1 year after disease onset (*P*=0.056) and thymic hyperplasia (*P*=0.036) were potentially associated with achievement of CSR. In the multivariable analysis, thymectomy before generalization (adjusted HR 3.42, 95% CI 1.74-6.71; *P*<0.001) was still associated with achievement of CSR after adjusting for age at disease onset, time from disease onset to thymectomy and thymic histopathology.

On the other hand, we continued working on this topic and tried to develop a prediction model for secondary generalization in MG patients with purely ocular symptoms at onset (unpublished data).

Four hundred and ninety-eight patients were reviewed, after a stepwise exclusion of 133 patients who did not fulfil the study criteria of MG diagnosis, 5 patients with missing data on the development of secondary generalization, 34 patients with unspecified time from symptoms onset to secondary generalization, 64 patients with a follow-up time less than 24

months and 9 patients who generalized within 3 months after symptoms onset, leaving 253 patients with a female:male ratio of 0.69 who were eligible for inclusion. With a median follow-up time of 81 (51-132) months, 113 patients developed secondary generalization, 140 patients did not. Figure 3 briefly shows the flowchart of the following study. The median age at MG onset was 61 (48-71) years. About half of the patients used corticosteroids agents before secondary generalization. Kaplan-Meier analysis showed that the estimated probability of generalization at 2 years was 26.4%.

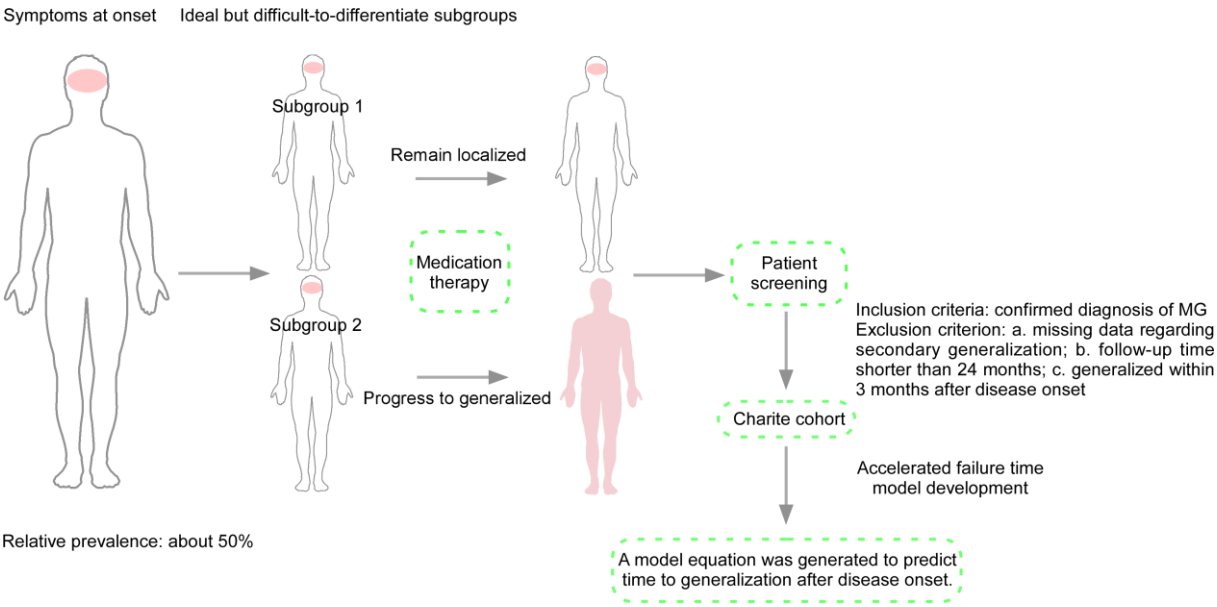

Figure 3. Flowchart of the following study. The pink color filled in the outlines represents the distribution of weakness, specifically localized ocular symptoms or generalized symptoms.

No non-linear effects were found in the two continuous variables, age at onset and anti-AChR antibody titer. However, there was a time-varying effect in the variable of age at onset (*P*=0.00252). In the log-normal AFT model, all the six variables were associated with the development of secondary generalization based on the change of Akaike's information criterion: gender (female vs male, TR 0.59, 95%CI 0.37-0.93, *p*=0.0237), age at onset (71 years vs 48 years, TR 0.72, 95%CI 0.53-0.98, *p*=0.0338), anti-AChR antibody titer (11.64 nM vs 0.32 nM, TR 0.68, 95%CI 0.54-0.85, *p*=0.0008), anti-MuSK antibody status (positive vs negative, TR 0.06, 95%CI 0.01-0.34, *p*=0.0013), presence of OAID (yes vs no, TR 0.61, 95%CI 0.34-1.07, *p*=0.0812) and use corticosteroids use (no vs yes, TR 0.40, 95%CI 0.26-0.62, *p*<0.0001). An increase in anti-AChR antibody titer from 0.32nM to 11.64 nM shortens the time to secondary generalization by 33% (95% CI 16%-46%). The discriminative ability of the final model for the development of secondary generalization was assessed using C-statistic (0.689).

A log-normal AFT model equation was then generated to calculate the cumulative probability of secondary generation at different time points based on these six variables:

$$\text{Prob}\{T<=t\} = \Phi[(\log(t) - X\beta)/1.455838], \text{ where}$$

$X\beta$ =6.644285 - 0.5251146[female] – 0.03436059[anti-AChR antibody titer] -2.7788343[anti-MuSK antibody positive] - 0.4998894[presence of OAID] – 0.01436344[age at disease onset] – 0.9193592[no corticosteroids use].

And [c]=1 if subject is in group, c, 0 otherwise. Φ is the cumulative normal distribution function; t=time (months). The median time to secondary generalization is exp ($X\beta$).

For example, a female patient with an age at MG onset of 40 years, who was seronegative for anti-MuSK antibody but seropositive for anti-AChR antibody (titer 10 nM), had Hashimoto's thyroiditis and took prednisone to control her diplopia. For this case:

$X\beta$ =6.644285 - 0.5251146*1 – 0.03436059*10 -2.7788343*0 - 0.4998894*1 – 0.01436344*40 – 0.9193592*0 = 4.7011375.

Thus, the median time to secondary generalization is exp (4.7011375), which equals 110.0723 months.

The 1-year generalization rate = Prob{T<=12} =Φ[(log(12) – 4.7011375.)/1.455838] = Φ(-1.5223057) = 0.06396625
The 2-year generalization rate = Prob{T<=24} =Φ[(log(24) – 4.7011375.)/1.455838] = Φ(-1.0461902) = 0.1477366
The 3-year generalization rate = Prob{T<=36} = Φ[(log(36) – 4.7011375.)/1.455838] = Φ(-0.7676805) = 0.2213385

The example showed in detail how to estimate the specific time to generalization and the probabilities of generalization at different time points for each patient. In addition to these three time points, the model equation could offer flexible predictions at any time point after disease onset.

Discussion

In this study, propensity score matching was performed to reduce the selection bias between the two groups, OMG group vs. gOMG group. The remission rate was higher in the OMG group than the gOMG group, which indicated that thymectomy before generalization might result in better clinical outcomes for patients with OMG, compared with thymectomy after generalization does. Moreover, the results were consistent in the nonthymomatous MG subgroup analyses.

From a historical point of view, thymectomy has gradually become a cornerstone of the treatment for MG since Schumacher and Roth reported a significant improvement of MG after removal of the thymus in a 18-year old woman with MG during the surgical treatment of hyperthyroidism by the celebrated surgeon Sauerbruch in 1911 (9). Later in 1936, the American surgeon Blalock removed a tumorous cystic lesion via transsternal thymectomy in a 21-year old woman, which resulted in a remarkable improvement of the associated MG (10). On the wave of enthusiasm, he attempted to further define the value of thymectomy in MG, performed transsternal thymectomies in patients with MG, and reported favorable results in a series of 6 patients in 1941 (11). In this study, Blalock also emphasized the radicality of transsternal approach to thymectomy, which is superior to transcervical approach given the anatomical location of the thymus. Three years later, Blalock found that the results of a larger series of 20 cases after thymectomy are not uniformly predictable, thus he lost interest in this project (12). These primary investigations, however, shed light on the therapeutic value of thymectomy in the treatment of MG and encouraged many surgeons to further explore the therapeutic value of thymectomy for MG (13, 14). In 1950s, a heated discussion of thymectomy in the treatment of MG was provoked by a nonrandomized controlled study from the Mayo Clinic. The results showed that the clinical outcomes favored thymectomy mainly due to a bias in patient selection, thus thymectomy might only be performed in patients with thymic tumors, but not those with nonthymomatous MG (14). While these results make some physicians and surgeons hesitate to recommend thymectomy for patients with MG, Keynes' good results supported the beneficial role of thymectomy for MG and promoted further research in this field (13). In 1966, a landmark study with a sample size of 1355 revealed that the clinical outcomes of patients who received surgical treatment is better than that of patients who received nonsurgical treatment (15). Besides, the results also indicated that the clinical outcomes favor patients with nonthymomatous MG, female sex, and younger than 40 years (15). Although it was still with considerable criticism and opposition, thymectomy was increasingly performed for patients with MG. In the late-1960s, cervical approach to thymectomy was revived in patients with MG,

because its less invasiveness than the transsternal approach (16). In 1977, Jaretzki performed a surgical anatomical study to investigate common anatomical variations of thymus, concluding that a combined approach of median sternotomy and cervicotomy is necessary for a total thymectomy (17). The results presented in this study opened up a spirited debate balancing the pros and cons of different surgical approaches. To resolve this controversy, Jaretzki did a comprehensive review of different approaches to thymectomy and compared the clinical outcomes following these different procedures (18). In this review, he pointed out that the more complete the resection, the better prognosis of MG. In 2000, while surgeons were trying to figure out the procedure of choice for MG, a subcommittee of the American Academy of Neurology conducted an evidence-based review on the efficacy of thymectomy for MG, demonstrating that the benefit of thymectomy for patients with nonthymomatous MG was not conclusively established yet (19). Not long after that, a randomized controlled trial about thymectomy for MG (MGTX) was planned and began accruing patients with nonthymomatous generalized MG (GMG) who are seropositive for anti-AChR antibody and have a disease duration less than 5 years (8). However, it was not until 2016 that the long-awaited results of the trial finally determined the therapeutic value of thymectomy for patients with GMG (8). Recently, the 5-year results of the trial revealed that thymectomy continues to confer benefits on these patients in terms of improving symptoms and reducing prednisone use (7). Currently, the controversy referring to the therapeutic value of thymectomy for MG was associated with several subgroups of MG, including juvenile MG, elderly MG, MG seronegative for anti-AChR antibody and OMG.

The evolution of thymectomy is also a history of surgical passion for modifying and improving the surgical approaches, thereby providing patients with MG better clinical outcomes (22). It is possible that different surgical approaches can result in different clinical outcomes (18). The authors prefer left-sided approach to robot-assisted thymectomy for several reasons: the left lobe is always larger and extends to or even across the left phrenic nerve (38); the presence of ectopic thymic tissue is more common at the area lateral to the left phrenic nerve than the area lateral to the right phrenic nerve (39); the anatomical variations of upper poles are not uncommon, such as the upper poles run cranially behind or even around the innominate vein (17). In general, the thymus gland and all fatty tissue between the phrenic nerves from the diaphragm up to the lower cervical area should be removed. Besides, extra attention should be paid to the common anatomical sites harboring ectopic thymic tissue: anterior mediastinum, pericardiophrenic angles, aortopulmonary window,

pretracheal area, aortocaval groove, lateral to phrenic nerves and behind innominate vein (40).

Our results showed that robot-assisted thymectomy was effective in nonthymomatous OMG patients with a 5-year CSR rate of 53.5%, which is in line with a recent systematic review and meta-analysis of different approaches to thymectomy for MG (41). Thus, it is nearly undeniable that thymectomy is an effective treatment for OMG patients in terms of inducing remission. However, several flaws of the existing studies weaken the conclusion, including the retrospective nature, small sample sizes, often lack of nonsurgical control and different definitions of remission. In a previous retrospective study comparing the efficacy of surgical treatment and nonsurgical treatment in the management of OMG, thymectomy is marginally associated with remission (23). Although all the existing studies have considerable limitations, these pieces of evidence should not be negated. It had been a similar situation with the role of thymectomy for GMG until the MGTX trial was available, but the results from the retrospective studies are consistent with that of the MGTX trial (7, 8).

Our results also indicated that thymectomy before generalization was able to result in a higher remission rate than thymectomy after generalization did. A main obstacle, which stands in the way of formulating a surgery plan for OMG, is the wait-and-see treatment strategy. Many patients with OMG are reluctant to receive the “aggressive” treatment until the time of generalization. Wait-and-see strategy may benefit patients who will achieve complete remission. However, the rate of spontaneous remission in OMG patients is only about 20% and the remission can last from 1 month to 20 years (2). Regarding spontaneous remission, about 65% patients experience complete remission (duration > 2 years), the rest only experience episodic remission. The time from symptoms onset to spontaneous remission varies from several months up to 13 years, of which 30% is less than 1 year (2). For patients who will develop secondary generalization, accepting this treatment strategy is tantamount to giving up the optimal timing of thymectomy, because thymectomy has been frequently proved to be more effective if performed early after disease onset (13, 23). Besides, many patients with OMG require corticosteroids agents to control the myasthenic symptoms, the steroid-sparing effect of thymectomy can be beneficial for them, thereby possibly decreasing the likelihood of concurrent side effects (23). Given the variable disease courses of OMG, thymectomy should be considered, at least for some, a treatment option before the development of secondary generalization.

Therefore, we suggest that thymectomy should be considered for OMG patients who are more likely to develop secondary generalization and do

not respond well to the corticosteroids agents or have intolerable side effects from them. However, it is now still difficult to predict whether a patient with OMG will develop secondary generalization or not. Our next study will focus on this topic, developing a prediction model to predict secondary generalization of OMG.

In the further study, we developed a prediction model to predict the secondary generalization of OMG, which included six clinical variables: gender, age at disease onset, anti-AChR antibody titer, anti-MuSK status, the presence of other autoimmune diseases (OAID) and use of corticosteroids. All the predictors are routinely available, which is convenient to use in the clinical practice. The model performance was fair according to a C-statistic of 0.689. The underline equations can provide both the physicians and patients a personalized time to generalization and the probabilities of generalization at different time point after disease onset.

The applicable criteria of the prediction model should be mentioned: confirmed diagnosis of OMG, time from symptoms onset to generalization > 3 months and no evidence of mediastinal tumor from the imaging findings. The prediction model assigns an estimated probability of the development of secondary generalization to patients with OMG based on the routine clinical variables. All the six clinical variables have been frequently reported in previous studies as risk factors for secondary generalization in patients with OMG (26-29). In a steroid-naïve cohort, seropositive for anti-AChR antibody and disease onset younger than 50 years are identified as risk factors for secondary generalization of OMG (26). Another previous study further addressed the role of the antibody titer in the secondary generalization, higher antibody titer indicates a higher risk of generalization (27). Besides, a recent study indicated that female sex, history of smoking and thymic abnormality are risk factors of secondary generalization in OMG patients with seropositive anti-AChR antibody (28). Furthermore, Wong also developed a score system to stratify the risk of generalization based on three clinical variables: seropositive for anti-AChR antibody, presence of comorbidities including autoimmune disease and thymic hyperplasia (29). Nevertheless, the combined predictive ability of these clinical variables has not been studied before. In contrast with the score system developed by Wong, the present study included a larger cohort and all the data were preserved in a well-constructed database. In addition, the model was rigorously developed and internally validated.

Stratifying the risk of generalization can help guide the clinical decision making, thereby possibly improving the clinical outcomes. The proposed equation might provide OMG patients an accurate probability of conversion to gOMG in an individualized manner. The treatment plan of

patients with different levels of risk can be then tailored to meet different individual needs. A more “aggressive” treatment plan containing corticosteroids agents or thymectomy can be recommended to improve the clinical outcomes and reduce the risk of generalization. While the role of corticosteroids agents in reducing the generalization rate of OMG has not been determined by well-designed clinical trials, some retrospective studies have shed light on that (4, 5). In the current study, our results also indicated that the use of corticosteroids agents was associated with the development of secondary generalization. A recent study recommended corticosteroids agents as an initial treatment for patients with OMG, however, even low to moderate dose of oral corticosteroid results in side effects in about 28% patients (6). Our results from the previous study indicated thymectomy before generalization might result in a higher remission rate than thymectomy after generalization did (25). Thus, thymectomy might be a treatment option for OMG patients with high risk of generalization who do not respond satisfactorily to corticosteroids agents or have intolerable side effects from them.

In the era of minimally invasive surgery, thymectomy has gone beyond large, painful transsternal incision in promise of enhanced recovery and excellent clinical outcomes (22). A recent systematic review and meta-analysis demonstrated that minimally invasive thymectomies are superior to the transsternal approach in terms of the perioperative outcomes (42). Besides, some previous studies also indicated that minimally invasive thymectomies do not compromise to clinical outcomes of patients with MG, compared to transsternal thymectomy (43, 44). Importantly, our previous study has shed light on the superiority of robot-assisted thymectomy over conventional thoracoscopic thymectomy in terms of inducing the remission of MG (45). Therefore, formulating a robot-assisted thymectomy plan should not intimidate OMG patients with a high risk of generalization.

In conclusion, several common clinical variables were identified as risk factors for generalization of OMG based on the large cohort. The proposed equation was able to estimate the probability of conversion to generalization at different time points. Further external validation will be performed to establish its value in predicting the development of secondary generalization in patients with purely ocular symptoms at MG onset.

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Affidavit
[Part of the dissertation]

Statutory Declaration

"I, [Feng, Li], by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic [Zur Bedeutung der roboterunterstützten Thymektomie bei Myasthenia gravis mit okulärem Symptombeginn; The importance of robot-assisted thymectomy in selected myasthenia gravis patients with purely ocular symptoms at onset], independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

[In the case of having conducted your doctoral research project completely or in part within a working group:] Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

Declaration of your own contribution to the publications

[Feng LI] contributed the following to the below listed publications:

Publikation 1: Thymectomy in ocular myasthenia gravis before generalization results in a higher remission rate
Beitrag im Einzelnen (bitte ausführlich ausführen):
This study was designed by JC Rueckert and F Li. F Li collected all the baseline characteristics and perioperative data from the hospital information system with the help of A Elsner, M Swierzy and M Ismail. After that, Prof. Rueckert and F Li asked several colleagues, ZM Li, G Bauer and D Uluk, to call the patients for the last follow-up. F Li performed all the statistical analyses with the help of YL Chen for the first version of the draft. Specifically, YL Chen did the propensity score matching using SPSS (IBM Corp, Armonk, USA), formulated the matched database, and prepared the description of the statistical method and the interpretation of the propensity score matching. F Li performed the rest statistical analyses. However, the reviewers and the editor asked us to improve the propensity score matching procedure at the time of revision. All the statistical analyses were then performed by R software (Vienna, Austria) with the help of Ulrike Grittner from the Department of Biostatistics and Clinical Epidemiology at the Charité Berlin. The propensity score matching was performed using ‘matchit’ package in R software. After matching, F Li formulated tables 1, 2, 3 and 4 in the Microsoft Office Word based on the baseline characteristics and the clinical outcomes. F Li made all the figures using the ‘survival’ and ‘ggplot2’ packages. Figures were combined using Canvas software (Canvas GFX, Ltd., Plantation, USA). However, all these statistical evaluation, tables and figures were then checked by YL Chen, JC Rueckert, A Meisel, M Ismail and M Swierzy. F Li modified all the tables and figures according to the comments from the coauthors. All the coauthors took part in the writing of the original draft and made critical revision of the manuscript. The final approval of the manuscript and submission to the European Journal of Cardiothoracic Surgery were made by all authors.

On the other hand, we continued our work to develop a prediction model of secondary generalization in myasthenia gravis patients with purely ocular symptoms at onset. We detailed the contribution to these results below.
Beitrag im Einzelnen (bitte ausführlich ausführen):

The further work was designed by JC Rueckert, A Meisel and F Li. HB Zhang collected all the clinical data from a nonsurgical MG database of the Integrated Myasthenia Gravis Center. F Li reviewed the medical records in the hospital information system to double check the clinical variables of all patients. F Li performed all the statistical analyses using R software with the help of Alberto Carmona-Bayonas (Hospital Universitario Morales Meseguer, Murcia, Spain). F Li explored the non-linear effect and time-varying effect using the generalized additive model in R software. F Li performed the multivariable analysis using log-normal accelerated failure time model in the R software with the ‘rms’ package. The equation was generated by F Li using the ‘rms’ package in R software. All the statistical analyses were then checked by JC Rueckert and A Meisel. The results have not been published but the authors would like to publish it in an international peer-reviewed journal in the future.

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Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

Excerpt of the Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"SURGERY"** Selected Category Scheme: WoS
Gesamtanzahl: 200 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	ANNALS OF SURGERY	48,932	9.203	0.066340
2	JAMA Surgery	4,515	8.498	0.024940
3	JOURNAL OF HEART AND LUNG TRANSPLANTATION	11,129	7.955	0.028970
4	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	29,695	7.144	0.032980
5	ENDOSCOPY	10,185	6.629	0.017400
6	AMERICAN JOURNAL OF TRANSPLANTATION	23,460	6.493	0.051290
7	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	20,873	5.878	0.023060
8	BRITISH JOURNAL OF SURGERY	22,899	5.433	0.031220
9	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	27,492	4.880	0.042650
10	JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS	16,326	4.767	0.031690
11	JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME	46,966	4.583	0.044930
12	NEUROSURGERY	28,592	4.475	0.025930
13	ARTHROSCOPY-THE JOURNAL OF ARTHROSCOPIC AND RELATED SURGERY	15,568	4.330	0.020760
14	JOURNAL OF NEUROSURGERY	34,561	4.318	0.030750
15	CLINICAL ORTHOPAEDICS AND RELATED RESEARCH	40,313	4.091	0.037880
16	TRANSPLANTATION	24,731	3.960	0.030960
17	Surgery for Obesity and Related Diseases	5,351	3.900	0.011660
18	OBESITY SURGERY	12,135	3.895	0.018350
19	EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY	8,352	3.877	0.012910
20	ANNALS OF SURGICAL ONCOLOGY	26,592	3.857	0.053440

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
20	ANNALS OF SURGICAL ONCOLOGY	26,592	3.857	0.053440
21	ANNALS OF THORACIC SURGERY	34,006	3.779	0.043550
22	LIVER TRANSPLANTATION	9,930	3.752	0.013900
23	Journal of Trauma and Acute Care Surgery	7,701	3.695	0.030340
24	EJSO	7,996	3.688	0.014750
25	DISEASES OF THE COLON & RECTUM	14,063	3.616	0.013470
26	Bone & Joint Journal	4,676	3.581	0.019010
27	SURGERY	19,394	3.574	0.026770
28	Journal of NeuroInterventional Surgery	3,454	3.524	0.010930
29	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	15,001	3.504	0.026110
30	PLASTIC AND RECONSTRUCTIVE SURGERY	34,285	3.475	0.032050
31	HEPATOBILIARY SURGERY AND NUTRITION	605	3.451	0.001980
32	Digestive Endoscopy	2,241	3.375	0.005690
33	JAMA Otolaryngology-Head & Neck Surgery	2,235	3.295	0.010200
34	JOURNAL OF VASCULAR SURGERY	24,792	3.294	0.030300
35	JOURNAL OF NEUROSURGICAL ANESTHESIOLOGY	1,607	3.238	0.002370
36	KNEE SURGERY SPORTS TRAUMATOLOGY ARTHROSCOPY	14,017	3.210	0.026090
37	World Journal of Emergency Surgery	997	3.198	0.002760
38	TRANSPLANT INTERNATIONAL	4,709	3.196	0.009890
39	Surgical Oncology Clinics of North America	1,139	3.178	0.002150
40	HPB	3,936	3.131	0.009110
41	SURGICAL ENDOSCOPY AND OTHER INTERVENTIONAL TECHNIQUES	20,301	3.117	0.034000

Selected JCR Year: 2017; Selected Categories: "SURGERY"

Appendix

Publication: Thymectomy in ocular myasthenia gravis before generalization results in a higher remission rate

Li F, Li Z, Chen Y, Bauer G, Uluk D, Elsner A, Swierzy M, Ismail M, Meisel A, Ruckert JC. Eur J Cardiothorac Surg 2020;57(3):478-487 https://doi.org/10.1093/ejcts/ezz275

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Curriculum vitae

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