Short-term outcomes, longer-term disability and relapse risk in LGI1-antibody encephalitis

Sudarshini Ramanathan,[1,2,†] John Soltys,[3,4,†] Sophia Michael,[2,†] Samuel V. Mackrill,[2] Jonathan Cleaver,[2] Robyn Williams,[2,3] Mateusz Makuch,[2,3] Patrick Waters,[2] Yaacov Ansizka,[2] Alessandro Dinoto,[2] Mohsen Farazdaghi,[2] Benjamin Trewin,[1] Jan Rudnik,[5] Panayotes Demakakos,[5] Stephen Yates,[5] Anais Thouin,[6] Sonam Dilwali,[7] Hyoshin Son,[8] Russell C. Dale,[9] Anu Jacob,[10,11] Andreas Lutterotti,[6,12] Ava Easton,[13,14] Adam E. Handel,[2] Michael D. Geschwind,[7] Jeffrey M. Gelfand,[7] Soon-Tae Lee,[8] Carsten Finke,[15] Sophie Binks,[2] Tomas Kalincik[16,17,‡] and Sarosh R. Irani[2,3,‡] on behalf of the International LGI1-antibody Encephalitis Consortium

[†,‡]**These authors contributed equally to this work.**

Abstract

Leucine-rich glioma-inactivated-1 antibody encephalitis (LGI1-Ab-E) is a common and immunotherapy-responsive form of encephalitis. However, it is not known which immunotherapy regimens improve short-term outcomes, longer-term disability and relapse risk. Further, it is not known if the widely-utilised modified Rankin Scale (mRS) accurately captures quality of life (QoL) in LGI1-Ab-E, complicating disability measurements and interpretation of immunotherapy responses.

A multicentre, international, real-world comparative analysis of patients with LGI1-Ab-E. Retrospective data from patient records evaluated short-term seizure and cognitive outcomes, 1-6 year disability, and future relapse risk associations, by integrating demographics, clinical features investigations and exposures to immunotherapies and antiseizure medications (ASMs). Patient- and neurologist-rated QoL assessments were used to establish an evidence-based mRS threshold for defining clinically significant disability. Cox proportional hazard models, Anderson-Gill, and generalised linear mixed-effects models were employed.

181 patients were included, with median age at onset 63 years (range 23 - 92); 122/181 (67%) were male. Short-term outcomes, evaluated at both five and ten weeks post-

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treatment initiation, identified exposure to immunotherapies associated with seizure resolution (OR=13.97, 95%CI=6.10-32.01; p<0.0001 and OR=8.53, 95%CI=4.14-17.55; p<0.0001, respectively), notably with corticosteroids, plasma exchange and rituximab, but not ASMs, intravenous immunoglobulins or steroid sparing agents. Conversely, seizure recurrence was observed after discontinuation of oral prednisolone, but not other immunotherapies or ASMs (OR=39.53, 95%CI=12.70-122.20, p<0.0001). To evaluate longer-term disability, first, mRS scores were calibrated using QoL assessments: this identified a significant increase in patient-rated disability at mRS score of 2. Hence, using mRS 0-1 as a favourable outcome, we identified worse mRS at nadir associated with greater one-year disability (OR=2.56, 95%CI=1.56–4.20, p=0.0003), and each month of delayed immunotherapy associated with a 16% increased risk of disability (HR=1.16, 95%CI=1.06-1.35, p=0.004). Additionally, absence of immunotherapy associated both with greater one-year disability (OR=5.67; 95% CI 1.19-26.54, p=0.03) and a relapsing course (OR=7.64, 95%CI=2.51-21.77, p=0.0002). Both a relapsing course, observed in 38% of patients, and the number of relapses associated with step-wise worsening of disability and QoL-outcomes. Rituximab exposure was the only identified clinical factor associated with reduced future relapse risk, by 93% (HR=0.07, 95%CI=0.01-0.48, p=0.002). Persistent serum LGI1-IgMs, but not LGI1-IgGs, at one-year, associated with future relapses (HR=11.69, 95%CI=1.58-145.80, p=0.02).

Distinctive clinical factors and select immunotherapies, particularly intravenous methylprednisolone and plasma exchange, but not ASMs, associated with favourable short-term outcomes, patient-centric longer-term disability and relapses in LGI1-Ab-E. Our findings provide evidence-based disability thresholds, highlight novel prognostic biomarkers, and pragmatically guide LGI1-Ab-E care, pending randomized clinical trials.

Author affiliations:

1 Translational Neuroimmunology Group, Kids Neuroscience Centre and ANZAC Research Institute, Department of Neurology, Concord Hospital; Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2139, Australia

2 Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, OX3 9DU, UK

3 Department of Neurology and Neurosciences, Mayo Clinic, Jacksonville, FL 32224, USA

4 Department of Neurology, University of South Alabama College of Medicine, Mobile, AL 36604, USA

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5 UCB Pharma, 208 Bath Road, Slough, SL1 3WE, UK

6 Clinical Department of Neurology, University Hospital of Zurich, 8091 Zurich, Switzerland

7 Department of Neurology, University of California, San Francisco, CA 94143, USA

8 Department of Neurology, Seoul National University Hospital, Seoul 03080, South Korea

9 Clinical Neuroimmunology Group, Kids Neuroscience Centre, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2145, Australia

10 Department of Neurology, The Walton Centre NHS Foundation Trust, Liverpool, L9 7LJ, UK

11 Department of Neurology, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE

12 Center for Clinical Neuroimmunology, Bellevue Medical Group, 8001 Zürich, Switzerland

13 Encephalitis International, Malton, North Yorkshire, YO17 7DT, UK

14 Department of Clinical Infection, Microbiology and Immunology, University of Liverpool, Liverpool, L69 7ZX, UK

15 Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, 10117, Germany

16 CORe, Department of Medicine, University of Melbourne, Parkville VIC 3050, Melbourne, Australia

17 Neuroimmunology Centre, Royal Melbourne Hospital, Melbourne, VIC 3000, Australia

Correspondence to: Professor Sarosh R. Irani

Departments of Neurology and Neurosciences, 4500 San Pablo Road, Mangurian Building, Jacksonville, FL 32224, USA

E-mail: irani.sarosh@mayo.edu

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Introduction

Leucine-rich glioma-inactivated-1 antibody encephalitis (LGI1-Ab-E) was first described in 2010, and now represents the most common cause of adult-onset autoimmune encephalitis (AE).[1-5] LGI1-Ab-E typically affects patients over sixty years, and classically associates with faciobrachial dystonic seizures (FBDS) and limbic encephalitis, although well-recognised clinical manisfestations extend to other seizure types, neuropsychiatric features, sleep dysfunction, and neuropathic pain.[1-3,6-10]

Despite these clinical advances, there is no consensus regarding management strategies. Overall, immunotherapies appear to improve LGI1-Ab-E patient outcomes, yet specific regimens are lacking. The only published RCT in LGI1-Ab-E showed modest seizure and cognitive improvements with intravenous immunoglobulins (IVIG) but was small and underpowered.[11] Retrospective studies suggest efficacy of corticosteroids.[12,13] Additionally, there are contradictory conclusions regarding the association of rituximab and oral steroid sparing agents (SSA) on future relapse risk.[14-18] This variability may arise from small, single-centre or country-based retrospective cohorts, regional immunotherapeutic approaches and access, limited follow up durations, methods used to control fro antiseizure medication (ASM) use, and variable consideration given to timeframes determining biological efficacy of immunotherapies.[6,9,13,19,20]

Complicating interpretation and translation, almost all studies have utilized modified Rankin Score (mRS) or neuropsychological metrics as disability outcomes.[3,6-9,13,14,21-25] However, these measures were not designed to capture residual personality changes, sleep disturbance and fatigue, major determinants of quality of life (QoL) in LGI1-Ab-E.[24,26-28]Furthermore, mRS scores ≤ 2 have represented "favourable" outcomes in LGI1-Ab-E and other forms of AE, without demonstration that this threshold accurately reflects changes in patient QoL.[2,9,10,14] Further, despite being reported in 20-60% of LGI1-Ab-E patients, the treatment of relapses and their contributions to disability accumulation are poorly understood.[6,9,10,13,29-31] Collectively, we hypothesised a patient-centric reappraisal of outcome measurements would offer more meaningful analyses of treatment associations with, and prognostic predictors of, disability accumulation.

Given the above multiple limitations of published retrospective studies, the premature termination of RCTs in LGI1-Ab-E,[11,32,33] the ongoing challenges in trial recruitment, and the

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inevitable lags to reporting findings from few, select medications within a necessarily restricted clinical setting,[32,34,35] we reasoned that rigorous analyses of multicentre real-world data are likely to provide valuable and urgently required pragmatic evidence to evaluate optimal immunotherapies.

Herein, we assembled a large multicentre, international cohort of LGI1-Ab-E patients to evaluate the efficacy and safety of immunotherapies and ASMs with respect to three key outcomes: short-term seizure control and cognition, longer-term disability, and relapse rates, incorporating patient QoL ratings to rethreshold mRS outcomes. Our data identify prognostic factors to guide treatment recommendations through chronological phases of the LGI1-Ab-E patient journey, and to better design prospective trials in this disease, with principles that can be translated to other forms of AE.

Materials and methods

Patient selection and clinical characterisation

Patients were identified with typical clinical features of LGI1-Ab-E and positive serum LGI1-antibodies, determined by commercial fixed cell-based assays (CBA), from eleven tertiary referral centres in the United Kingdom (UK), South Korea, United States of America (USA), Germany, Switzerland and Australia (Fig.1, Fig.S1 and Table S1). Non-UK centres were selected to include patients with a variety of non corticosteroid immunotherapy exposures, mostly unavailable within the UK National Health System. Each centre retrospectively extracted clinical and paraclinical data from patient records into a standardised database (Table S2). Paraclinical features included hyponatremia (sodium <135 mEq/L), inflammatory CSF (elevated white count, elevated protein, intrathecal immunoglobulin synthesis, >2 CSF, restricted bands or CSF LGI1-IgG), abnormal EEG (epileptiform discharges, epileptic seizures, or encephalopathic changes), and abnormal MRI (T2 hyperintensities/oedema in limbic regions).

The study was approved by the relevant local ethics approvals (UK REC16/YH/0013 and 15/LO/1433, Australia HREC2024/ETHO1205, Switzerland BASEC-Nr. 2020-01187, South Korea 1402-047-555/1705-130-856, Germany EA4/011/19, USA IRB 10-00526). SR, JS and SM compiled the standardised database.

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Study outcomes

The main three outcomes (Fig 1B) evaluated were: A) Short term: seizures and cognition at five and ten weeks post-treatment, using a semi-quantitative score advanced from the only published RCT in LGI1-Ab-E:[11] worsening or treatment escalation, no improvement, <50% improvement, >50% improvement or complete recovery; B) Longer-term disability using: i) longitudinal mRS data at 1, 2, 4 and 6 years, and ii) patient-QoL surveys, in a subset of UK patients and neurologists/carers who underwent in person or telephone interviews to score QoL from 1-100% their function at last follow-up where 100% reflected their premorbid status, and these data were used to determine favourable versus unfavourable mRS cut-offs; C) Relapse associations with disability and treatments, where a relapse was defined as new focal or multifocal central nervous system symptoms and/or signs lasting > 24 hours, following a minimum of 10 weeks of clinical stability, in the absence of a preferred alternative explanation.

Treatment exposures

Exposures of interest were specific ASMs or immunotherapies. Immunotherapies included intravenous methylprednisolone (IVMP), oral prednisolone (OP), IVIG, plasma exchange (PLEX), rituximab, and SSAs (including mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, cyclophosphamide, tocilizumab, cyclosporin). The duration of exposure to a particular immunotherapy was predefined as the period of adjudicated biological efficacy including the therapeutic lag from commencement, and persistent effects after cessation, as determined by lead authors (SR, JS, TK, SRI) following literature review and treatment experiences (Table S3).[36] A single course of rituximab was defined as exposure for 6 months. Medications discontinued prior to onset of biological efficacy, for example, due to intolerable side effects, were not considered exposures within treatment outcome analyses.

Adverse effects were rated using Common Terminology Criteria for Adverse Events gradings (CTCAE V.5.0), by a neurologist (MF) provided only with a description of the adverse effect, blinded to the medication. It was at the discretion of the reporting neurologist to attribute an adverse effect to any given medication.

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Statistical models first included broader groupings of either immunotherapies or ASMs, followed by stratification by individual medication exposures to achieve acceptable model fit, particularly for medications with fewer overall exposures. For ASMs, phenytoin, lorazepam, pregabalin, gabapentin, oxcarbazepine, clonazepam, topiramate, phenobarbital, eslicarbazepine, and piracetam were grouped as 'other'. For immunotherapies, SSAs, as above. Immunotherapy and ASM weaning was defined as any decrease in medication doses.

Statistical analyses

Statistical analyses were performed (Fig.1B) and figures generated using R (V4.5.1), MatLab (R2024b) and Prism V10 (GraphPad). All patients were included in descriptive analyses including demographics, clinical features, medication exposures and adverse effects, five and ten-week seizure and cognitive outcomes, sequential mRS and relapse dates. Medians and ranges were calculated for continuous variables, and frequencies and percentages were calculated for categorical variables. Data missingness resulted in varied final patient numbers across analyses (shown in Fig.1B).

Hypotheses were tested with Cox proportional hazards models (with proportionality of hazards evaluated by inspection of residuals), generalised linear mixed models (adjusted for demographic information where appropriate and for the participating centre[37]), and Andersen-Gill survival models, which account for recurrent events, prior exposures, changes in dosing or changing treatment exposures. Fixed terms were used to study associations of interest (relapse, favourable mRS score, seizure improvement, cognitive improvement), and to adjust models for potential confounders of associations of interest (onset age, nadir mRS, time to treatment, relapse, and all individual treatments, clinical, or paraclinical data). Mixed effect models were employed with patient identification as a random intercept to account for interdependence of observations. Propensity matching was performed in R software using the package MatchIt,[38] with caliper 0.1 and 1:1 matching. Firth's correction was applied where relevant to account for imperfect separation of exposure and outcome due to sample size. Two-sided students t-tests, Fisher's exact, and Mann-Whitney U test were used for analyses involving continuous or ranked variables as appropriate. Exact p-values are stated for all models.[39]

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LGI1-antibody measurements

In brief, sera from UK patients were incubated with LGI1-EGFP expressing transfected HEK cells for 30 minutes, and detected using anti-human IgG or IgM fluorophore tagged secondary antibodies, with fluorescence intensity quantified using fluorescence microscopy or flow cytometry, as previously described[10]. To determine end point dilutions, two-fold serial dilutions were performed until the last point of detection: 50 healthy and disease controls showed no binding. LGI1-IgG1 and LGI1-IgG4 quantifications were performed by flow cytometry.[10] Additionally, using methods developed when studying AQP4- and NMDAR-antibodies,[40,41] LGI1-IgMs were determined as present or absent after IgGs were fully absorbed using Protein G beads. For relapse correlations, the sample time-matched most closely with the relapse was analysed, and was required to be at least three months from the relapse. HLA Class II genotypes were evaluated from 70 UK patients, as previously described.[42]

Results

Demographics and clinical features

A total of 181 LGI1-Ab-E patients were identified across the UK (n=107), SK (n=24), US (n=15), Germany (n=14), Switzerland (n=11), and Australia (n=10), and showed consistency in median age of onset (median 63 years; range 23-92), male predilection (67%; 122/181), clinical features, relapse rates (38% with ≥1 relapse; 68/181) and duration of follow-up (median 3.4 years; range 0.3-15 years; Fig.1, Table 1 and S1). Expected variations in immunotherapy exposures and nadir mRS across centres (range 1-5; Fig.S2, Table S1) led to adjustment for centre as a variable in generalised linear modeling. Presenting features included cognitive impairment (93%, 168/181), seizures (all: 89%, 161/181, divided into FBDS, 53%, 96/181; other focal seizures: 78%, 141/181), psychiatric/behavioural (59%, 107/181) and sleep dysfunction (52%, 94/181; Fig.1A, Table 1, Fig.S1). 24% (44/181) of patients had a history of autoimmunity, 13% (24/181) had tumours and, in the UK cohort, concomitant autoantibodies were present in 8% (9/107; Fig.S3).

Exposures and adverse effects of ASMs and immunotherapies

Overall, 150/181 (83%) patients were exposed to ASMs (median n=1, range 0-6), and 177/181 (98%) to immunotherapies (median n=3, range 0-8; Fig.2A & Fig.S2). As initial

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treatments, 59/177 (33%) received ASMs alone, 65/177 (37%) immunotherapy alone and 53/177 (30%) received combinations of ASMs and immunotherapies (Fig.2B). The most common immunotherapy exposures at any disease stage included OP, IVMP, IVIG, rituximab and PLEX; with less frequent use of SSAs (Fig.2C, Fig.S4 and Table S4).

CTCAE gradings 1-3 occurred in 124/713 (17%) total immunotherapy exposures and 58/324 (18%) ASM exposures (Fig.2C & Fig.S4-5) and, overall, 123/157 (78%) patients had at least one adverse event. Disproportionate to other immunotherapies, adverse events were reported in 93/180 (52%) OP exposures, associated with metabolic, endocrine or neurological adverse effects (86/93 were CTCAE grade 1), 6/21 (29%) azathioprine exposures (5/6 CTCAE grade 1), and 8/79 (10%) rituximab exposures (all CTCAE grade 1, of which one was infectious). In contrast, adverse events less frequently associated with IVMP (5/164, 3%), IVIG (4/126, 3%) and PLEX (4/85, 5%). Levetiracetam was the most frequently used ASM, with 26/99 (26%) exposures associated with adverse events (23/26 CTCAE grade 1). Notable ASM complications included mood disturbances (16/64, 25%), rashes (14/64, 22%) and varied neurological AEs with CTCAE grade 2 events including polydipsia, nystagmus and suicidal ideation (Fig.S5).

Specific immunotherapies, but not ASMs, associate with improved short term outcomes

Change and resolution of seizures and cognition were evaluated at five and ten weeks post-treatment initiation (Fig.3, Table S4-6). Immunotherapies collectively associated with seizure freedom at both timepoints, independent of time to treatment initiation (OR=13.97, 95% CI 6.10-32.01; p<0.0001 and OR=8.53, 95% CI 4.14-17.55; p<0.0001, respectively, Fig.3A, Table S4). By contrast, no associations were observed between ASM exposure and seizure improvement. In multivariable comparisons of individual therapies, seizure freedom at both timepoints most favourably associated with corticosteroids (both IVMP and OP), PLEX and rituximab, but not with SSAs or any ASM, and negatively with IVIG (Fig.3B-C, Fig S6; Table S5). Further, propensity matching between patients receiving OP alone versus IVIG and OP, matched for onset age, sex, nadir mRS, time to immunotherapy and prior immunotherapy exposures, demonstrated that additional exposure to IVIG did not associate with benefit at either timepoint (OR=0.88, 95% CI 0.68–1.14, p=0.33 and OR=0.70, 95% CI 0.56–1.10, p=0.17, respectively, Fig.S6C). For short-term cognition, collective benefits neither associated with ASMs nor immunotherapies (Fig.3A, Table S4)

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although, individually, oral prednisolone, rituximab and SSAs associated with decreased likelihood of cognitive worsening at both five and ten weeks (Fig.3B-C, Fig S6B, Table S6).

Conversely, within 30 days of medication withdrawal, seizure recurrence only occurred after weaning of OP (72/159 exposures; 45%), not other immunotherapies, and rarely after ASMs (3/103, 3%; Fisher's exact, OR=39.53, 95% CI 12.70-122.20, p<0.0001, Fig.3D), despite similar durations of treatment exposure prior to wean (ANOVA with multiple comparisons, p=0.38, Fig.3E).

Patient-rated QoL recalibrates mRS 0-1 as a favourable disability outcome

To assess disability, first, we calibrated mRS thresholds to reflect patient-rated QoL. In most AE studies, mRS scores of 0-2 have been arbitrarily assigned as favourable outcomes.[2,9,10,14] To analyse this for the first-time in LGI1-Ab-E, we evaluated patient-and neurologist-perceived recovery ratings at last follow-up in the UK cohort (median 3.5 years; range 0.3-14.9; Table S1), where 100% represented complete recovery from premorbid function. For both assessments, mRS scores of 0 and 1 were statistically similar, but differed from mRS scores 2-5 (Fig.4A, ANOVA with multiple comparisons, all p<0.0026). This pattern was retained in patients with both less and more than the median duration of 3.5 years of follow-up (Fig.S7A). Thus, mRS distributions of 0-1 and 2-6 most closely represent patient-centric favourable versus unfavourable outcomes in LGI1-Ab-E, with good reliability observed between neurologist/carer and patient ratings (Pearson r=0.85, Fig.4B). Upon comparing these revised mRS thresholds to the traditional favourable versus unfavourable definitions (mRS ≤2 versus >2), the overall proportion of patients identified as having a favourable outcome at one-year reduced by ~50%, for both monophasic and relapsing cohorts, assessed both with and without the UK patients (Fig.4C, Fig.S7B, n=133). These differences were not observed with more arbitrarily defined cut-offs, which did not utilize patient-rated data (Fig.S7C). Taken together, these revised favourable vs unfavourable thesholds are driven by patient QoL ratings and, by comparison to traditional mRS cut offs, appear more representative of the frequent residual deficits observed in multifaceted dedicated evaluations of LGI1-Ab-E patient functional outcomes.[26,28]

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Long-term outcomes associate with disability at presentation and timing of any immunotherapy

Applying these disability-focused thresholds to our overall cohort, immunotherapy exposure associated with favourable mRS outcomes (mRS 0-1) at one-year (Fig.5A, OR=5.67; 95% CI 1.19-26.54, p=0.03), an effect not observed upon employing reported definitions of favourable mRS (0-2; Fig.5A, OR=1.09, 95% CI 0.34-3.43, p=0.99). After multivariable adjustment for candidate prognostic features or individual immunotherapies,[10,13,14,18,22] each month of immunotherapy delay associated with a 16% increased risk of unfavourable outcome (HR=1.16, 95% CI 1.06-1.35, p=0.004), equating to an OR of 1.01 (95% CI 1.002-1.010, p=0.0004) for each day of immunotherapy delay. Additionally, a higher nadir mRS independently associated with an unfavourable outcome (OR=2.56, 95% CI 1.56–4.20, p=0.0003; Fig.5B). HLA, tumour presence, and concomitant autoantibodies showed no associations with outcome (Fig.S7D-E). Again, immunotherapy associations were not observed when applying previously reported favourable mRS cut-offs of 0-2 vs 3-6 (Fig.S7F). Consistent with this model, the proportion of favourable to unfavourable outcomes was greatest when immunotherapies were initiated closest to disease onset (ratio 1.20), falling to 0.65 after 200 days (Fig.5C). Longitudinally, comparison of mRS outcomes at year 1 to those at year 2 (n=110), year 4 (n=65) and year 6 (n=40) revealed stability in 81%, 77% and 57% of patients, improvements in 16%, 20% and 43%, and deterioration in 4%, 6% and 0%, respectively (Fig.S8A-C).

Relapses associated with increased disability

Next, we analysed how relapses associated with longer-term disability. Monophasic courses associated with superior mRS distributions at last follow-up (Kruskal-Wallis test, p=0.007) and more ultimately associated with favourable mRS outcomes (OR=2.10, 95% CI 1.15-3.89; p=0.03, Fig.6A), despite similar mRS at nadir of the onset episode compared to relapsing patients (Fig.6B; Kruskal-Wallis test, p=0.22). Concordantly, relapses associated with poorer outcomes in patient and neurologist/carer QoL ratings (Students t-test, p=0.01 and p=0.03, respectively; Fig.6C). Each relapse associated with a stepwise accumulation of disability (1 versus both 2 or ≥3 relapses; Kruskal-Wallis tests, p=0.005 and p=0.008 respectively, Fig.6D), again unrelated to mRS at relapse nadir (Fig.6E). Further, in the 40 patients followed for six years, monophasic trajectories showed ongoing recovery up to six years, whereas, in relapsing patients, recovery plateaued at four years with fewer favourable mRS scores (Kruskal-Wallis test, p=0.047, Fig.6F). Again, traditional thresholds of mRS obscured some of these associations (Fig.S9). In summary, patients with

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monophasic disease show ongoing improvement through four to six years; while relapses associated with increased patient- and clinician-rated disability, worse long term recovery, and step-wise increases in disability.

Relapse risk reduced with rituximab, and increased with prednisone weaning

Given the association observed between more relapses and less favourable outcomes, we asked if immunotherapy exposure associated with risk of future relapse. Overall, absence of immunotherapy exposure during the onset episode more frequently associated with a relapsing disease course (53/162 (33%) versus 15/19 (79%); OR=7.64, 95% CI 2.51-21.77, p=0.0002; Fig.7A), independent of median time to relapse (Fig.S10). Rituximab was the only identified factor that associated with a lower risk for future relapse (93% reduction, HR=0.07, 95% CI 0.01-0.48, p=0.002, Fig.7B), without a discernible additional effect of multiple rituximab courses (Fig.S11A). Further, no relapses occurred during rituximab exposure (Table S8). An exploratory analysis revealed that the decision to trial an additional subsequent rescue immunotherapy was made least frequently with rituximab (10/79, 13%), whereas it reached 57% after IVIG and 50% after OP (Fig.7C). Further, at 6 years, unfavourable outcomes remained associated with relapse in rituximab-naïve patients (Fig.S11C). HLA, tumour presence, and concomitant autoantibodies did not associate with future relapse risk (Fig.S11D-E).

While our data suggest corticosteroids did not associate with reduced future relapse risk, relapses upon weaning OP (Fig.3D), clinical experiences and trial designs reflect the observation that exacerbations are precipitated by OP weaning.[7,11,32,43] Indeed, weaning OP was associated with an increased risk of relapse within the following 30 days (HR=4.72, 95% CI 1.42 – 15.74, p=0.01, Fig.7D), especially at daily doses under 30 mg (Fig.7E). However, dosing duration (Fig.3E), absolute dose thresholds or cumulative dose did not associate with reduced relapses (Fig.S12A-B, Andersen-Gill survival, all p >0.05). In summary, rituximab was the only immunotherapy associated with reduced future relapse risk, whereas OP weaning associated with an increased future relape risk.

LGI1-IgG and LGI1-IgM as biomarkers of relapses

Finally, with the aim of informing prognostication, modelling approaches identified very few biologically-plausible clinical or paraclinical biomarkers which associated with favourable

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mRS outcomes or relapses (Fig.S13). Hence, given LGI1-Ab-E is an autoantibody-mediated condition,[44,45] LGI1-antibody levels were explored. From 49 patients, multivariate analyses showed no LGI1-antibody associations with favorable outcomes at year 1 (Fig.7F). However, an increased risk for future relapses (Fig.7G) was associated with higher LGI1-IgG levels at the onset episode (>1:640 end point dilutions; HR=3.41 95% CI 1.18–9.32, p=0.03) and with detectable LGI1-IgM at 1 year (HR=11.69, 95% CI 1.58-145.80, p=0.02), independent of LGI1 IgG1/4 subclass levels (Fig.S14). This is analogous to prior work in neuromyelitis optica spectrum disorders,[40] and, in univariate analyses, we confirmed that persistent LGI1-IgM, but not persistent LGI1-IgG, after year one associated with future relapses, as all five patients with a detected LGI1-IgM later relapsed (Fisher's test, p=0.0007; Fig.7H).

Discussion

This study provides comprehensive multicentre international evidence identifying differential associations of individual immunotherapies to pragmatically guide the management of short-term seizure and cognitive outcomes, longer-term patient-rated disability and relapse risk in LGI1-Ab-E. Specifically, corticosteroids, PLEX and rituximab all associated with greater short-term seizure freedom, with no observed benefit from IVIG or ASMs. Consistent with this, weaning of OP, but not ASMs, associated with exacerbations. Timing of immunotherapy was the major modifiable factor associated with longer-term disability, albeit not with shorter-term outcomes. Relapses associated with increased disability in a dose-response manner, and were reduced with rituximab exposure. Moreover, our data fundamentally recalibrate measures of favourable outcomes in LGI1-Ab-E, consequently uncovering otherwise obscured observations regarding both long-term outcomes and relapses, and identifying a revised QoL-centric threshold of mRS for future studies, and for critical re-appraisals of previously reported treatment effect sizes.

Selection of immunotherapies for short-term benefit

Despite a beneficial, albeit modest, effect of IVIG in one LGI1-Ab-E RCT, our data suggest IVIG may not help with short-term seizure control, a finding aligned with several small retrospective studies.[12,13,15] However, propensity analysis did not confirm a beneficial or detrimental effect of IVIG on short-term seizure outcomes. On the other hand, the clear reduction in seizure activity associated with corticosteroids and PLEX is consistent with observations from our clinical practice, and supports their preferential use as first-line

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therapies in LGI1-Ab-E. Yet, frequent adverse effects, particularly from OP, mandate carefully considered administration of corticosteroids, and may support preferential use of IVMP given its markedly lower rate of adverse effects. The relatively rapid reductions of seizures and cognition with rituximab are surprising, and contrast with reports identifying seizure remission after second line immunotherapies after lags of several months.[17] Yet, this speed may be biologically intuitive if these relatively CNS-impenetrant therapeutic antibodies dominantly modulate peripheral immunity.[40] Yet, a beneficial effect of SSAs on cognition at five weeks appears earlier than predicted time to biological efficacy, and may represent fragility of modelling with small patient numbers. Also, differential effects on seizures versus cognition may reflect the multiple factors contained within a cognitive outcome, including effects of seizures themselves and encephalopathy. By contrast to immunotherapies, ASMs showed no associations with seizure control, their weaning rarely predisposed to relapses and all showed tendencies to associate with worsened cognition, alongside established frequent adverse effects.[7,42] Hence, our data support a very limited role for the administration of ASMs and IVIG in LGI1-Ab-E, with corticosteroids – particularly IVMP - and PLEX likely more beneficial.

Calibration of mRS thresholds

A patient-QoL centric approach led us to rethreshold favourable outcomes in LGI1-Ab-E as mRS 0-1, rather than either the traditional 0-2 reported in the literature or more arbitrary cut-offs. By inevitably reducing the overall proportion of favourable outcomes, this cut-off more closely aligns with QoL studies which indicate that LGI1-Ab-E patients often show multiple common impactful residual deficits and only a small proportion return to premorbid function.[8,9,14,26,46] Moreover, leveraging this recalibrated metric to evaluate the association between immunotherapy and clinically relevant outcomes, highlighted associations with disability and relapses which would have otherwise been obscured. These findings suggest historical estimates of recovery from LGI1-Ab-E were inflated, and our more conservative cut-off should be applied to critical re-analyses of datasets which, together with improved measurement tools including emerging patient reported outcome measures,[24,47,48] should more accurately enable evaluation of outcomes in LGI1-Ab-E.

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Selection of immunotherapies for longer-term benefits, including relapses

While absence of immunotherapy associated with poorer disability and relapse outcomes, no single immunotherapy appeared to associate with improved mRS. Yet, overall earlier administration of immunotherapies was associated with improved one-year outcome, with every day of delay producing quantifiable impacts. While some studies have not observed delays in immunotherapy associating with worse mRS and cognition, our data concur with many others and prompt further emphasis on physician education and the fundamental importance of early clinical recognition in LGI1-Ab-E.[1] Further, our outcome data highlighted functional improvements in LGI1-Ab-E continue for four to six years, providing valuable prognostic counselling advice, and hope, for our patients.

A relapsing course also associated with increased disability, both as measured by mRS and patient-QoL ratings. Further, the level of disability was proportional to the number of relapses experienced. Although often considered monophasic, 20-60% of LGI1-Ab-E patients may relapse.[6,9,10,30,31] Hence, our data highlight LGI1-Ab-E should be included amongst neuroimmune diseases with substantial disability secondary to frequent relapses and our observed 79% rate of relapses without immunotherapy suggest immunotherapies may prevent some relapses. Indeed, ritxumab showed a striking effect size in relapse prevention, echoed in smaller papers but not observed in more comprehensive studies.[14-16] Further, its relatively limited side effect profile highlights rituximab as a potentially critical preventative candidate for future treatment recommendations in LGI1-Ab-E, as in NMDAR-Ab-E, where rituximab has been demonstrated to improve both disability and reduce relapse rates.[49] Prior studies have suggested corticosteroids and mycophenolate mofetil may be effective in preventing relapses in LGI1-Ab-E, which we did not observe.[18,29] Additionally, in this study, IVIG administration was associated with the greatest use of rescue therapies and least beneficial short term effects, suggesting alterative options may be advantageous.

LGI1-IgM as a potential relapse biomarker

Given the potential for select immunotherapies to prevent relapses in LGI1-Ab-E, we sought biomarkers to guide their rational administration.[10,29] While very few statistically significant clinical or investigation parameters were observed, LGI1-IgG levels and, more strikingly, LGI1-IgMs carried some predictive value, analogous to findings in NMOSD,[40]

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whereas IgG1-4 subclasses did not show similar associations.[10] This finding requires validation but has biological implciations: that *de novo* immunizations against LGI1 may underlie relapses, and potentially implicate repopulation of LGI1-reactive B cells, rather than reactivation of pre-existing cells, mediate relapses in LGI1-Ab-E.[50]

Limitations

Limitations of our work include the retrospective design with inherent potential for selection bias, treatment indication bias, recall bias and informative censoring. Also, the definition of relapses after ten weeks of stability differs from some published definitions,[29] but is consistent with other diseases and, currently, all remain arbitrary. While our cohort appeared clinically homogeneous, the study participants, their presentations and outcomes may show heterogeneity across the participating centres. To mitigate this, we accounted for the study centre during analyses. Also, heterogeneity may have been accentuated by merging patients on similar classes of drugs, such as SSAs, a limitation which could be overcome with greater future sample sizes. Further, propensity methods were only applied to selected analyses and treatment effect estimates may be susceptible to confounding by indication. Formal cognitive assessments were not reported at 5 and 10-week timepoints, potentially masking more subtle treatment benefits, and our assessments of cognitive improvements should be more precisely quantified in future studies. Such studies might also incorporate a global false discovery approach to account for multiple analysis across independent and dependent variables. Longer-term follow up was available, albeit for increasingly diminishing numbers of patients. Strengths include the largest international collation of LGI1-Ab-E patients recruited from 11 centres in six countries, suggesting global generalisability, the granular nature of collected data on therapy and outcomes, the rethresholding of a long-standing measure in the field, and statistical models which adjust for potential confounders of treatment effects and for length to biological effect of immunotherapies.

Conclusions

In summary, our findings inform and substantially contribute to therapeutic strategies to optimise short-term and longer-term disability and relapse outcomes in LGI1-Ab-E. The rarity of this disorder and difficulties in recruitment of immunotherapy-naïve patients early in disease course have proven major challenges to RCT attempts.[11,32,33] Thus, to ultimately provide the robust evidence towards urgently improving patient care in LGI1-Ab-E and

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simultaneously inform future trial designs, we propose the need to continue to combine rigorous real-world registry data analysis in parallel with development of prognostic biomarkers, and advance and validate patient-reported outcome measures.[26,28,29,34] We anticipate this combination of approaches will ensure improved outcomes for the commonest adult-onset form of AE.[1]

Data availability

Deidentified clinical data collected for the study may be shared with requesting researchers following a signed data access agreement.

Funding

SR has received funding from National Health and Medical Research Council, Australia. She is a Snow Medical Fellow. She serves as a consultant on an advisory board for UCB and Limbic Neurology and has been an invited speaker for educational/research sessions coordinated by Biogen, Alexion, UCB, Novartis, Excemed and Limbic Neurology. She is on the medical advisory board (non-remunerated positions) of The MOG Project and the Sumaira Foundation. She is supported by an NHMRC Investigator Grant (GNT2008339). JS is supported by the Pete and Ashley Jones Endowment for autoimmune encephalitis research. AEH is supported by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre (BRC), the UK Medical Research Council-UKRI (United Kingdom) [MR/X022013/1] and MyAware. SR is supported by the National Health and Medical Research Council (NHMRC, Australia), the Petre Foundation, the Brain Foundation, the Royal Australasian College of Physicians, and the University of Sydney. MDG was supported by NIH/NIA R01 AG031189 and the Michael J. Homer Family fund. TK is supported by the National Health and Medical Research Council [2026836] and Multiple Sclerosis Australia. SRI is supported by the Wellcome (104079/Z/14/Z), the Medical Research Council (MRC) (MR/V007173/1), by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) and the Mayo Clinic Robert and Arlene Kogod Center on Aging [Aging Nervous System, 2024]. UCB funding supported part of this study. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript (AAM)

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version arising from this submission. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests

SR serves as a consultant on an advisory board for UCB and Limbic Neurology and has been an invited speaker for educational/research sessions coordinated by Biogen, Alexion, UCB, Novartis, Excemed and Limbic Neurology. STL has served on advisory boards for Roche, Argenx, Arialys Therapeutics, Advanced Neural Technologies and Piehealthcare. He is a named inventor of the CASE score. AL is an employee, co-founder and shareholder of Cellerys, a company pursuing antigen specific immune tolerance in multiple sclerosis. He is an inventor on patents for antigen-specific tolerization with peptide-coupled cells. He previously received financial compensation and/or travel support for lectures and advisory boards for from Almirall, Bayer, Biogen, BMS/Celgene, Genzyme/Sanofi, Merck, and Novartis. MDG has received consulting fees from IDRConsulting, AlphaSights LTD, Biohaven Pharmaceuticals, Gate Biosciences, Regeneron, Gerson Lehrman Group, BrainStorm Cell Therapeutics, Walter Grubb, Inc., Reata Pharmaceuticals, Inc., and MedConnect Pro, LLC, and honoraria from Eli Lilly outside the submitted work. TK served on scientific advisory boards or as a consultant for MS International Federation and World Health Organisation, Therapeutic Goods Administration, Sanofi, BMS, Roche, Janssen, Genzyme, Novartis, Merck and Biogen, received conference travel support and/or speaker honoraria from WebMD Global, Merck, Sandoz, Novartis, Biogen, Roche, Eisai, Genzyme, Teva and BioCSL and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene, Merck and Alexion. SRI has received honoraria/research support from Amgen, Argenx, Alexion, Atheneum, AstraZeneca, UCB, Roche, Janssen, IQVIA, Clarivate, Slingshot Insights, Slingshot, Cerebral therapeutics, BioHaven therapeutics, CSL Behring, and ONO Pharma, and receives licensed royalties on patent application WO/2010/046716 entitled 'Neurological Autoimmune Disorders', and has filed two other patents entitled “Diagnostic method and therapy” (WO2019211633 and US app 17/051,930; PCT application WO202189788A1) and “Biomarkers” (WO202189788A1, US App 18/279,624; PCT/GB2022/050614). JR and PD are employees of UCB. SY was an employee of UCB at the time of the study and is a stockholder of UCB.

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Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

International LGI1-antibody Encephalitis Consortium

Julia Thompson, Mian Bi, Todd A. Hardy, Ming Wei Lin, Sanjay Swaminathan, Andrew Bleasel, Stephen W. Reddel, Michael Johnson, Isabel Leite, Paul Maddison, Jan Coebergh, Saiju Jacob.

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Figure Legends

Figure 1 Study demographics. (A) Patient demographics and clinical features are depicted by clinical course and centre. For all circle plots, the solid line indicates median. (B) Flow chart depicts the overall study design plus the figures, principal models and number of patients included in each analysis. mRS = modified Rankin score, FBDS = faciobrachial dystonic seizure.

Figure 2 Medication exposures and adverse events. (A) Bar plot depicting total number of patients exposed to immunotherapies (IT) and antiseizure medications (ASM). (B) Pie graph depicting various combinations of initial ITs (shaded) and ASMs (patterned). One patient who initially received an antidepressant was excluded. (C) Pie charts depicting the number of initial (black) and subsequent (white) exposures for each immunotherapy. (D) Proportion of adverse effects graded by common terminology for clinical adverse effect (CTCAE 1-3) scores for 157 patients (not reported by one centre). Numbers of CTCAE events and total exposures differ as some patients developed multiple CTCAE events from a single exposure. ASM = anti-seizure medication, IVIG = intravenous immunoglobulin, IVMP = intravenous methylprednisolone, IT = immunotherapy, OP = oral prednisolone, PLEX = plasma exchange, RTX = rituximab, SSA = steroid sparing agent.

Figure 3 Short-term seizure and cognitive outcomes. (A) Effects on seizures (top, n=123) and cognition (bottom, n=146) following exposure to classes of immunotherapy (IT) or anti-seizure medications (ASM) (*p<0.05, Table S4 lists individual p values, Cox proportional hazards). Time to initiation of either IT or ASM did not influence 5 and 10 week responses. (B) and (C) depict respective responses at 5 and 10-weeks following treatment initiation, broken down by individual medication exposures (generalized linear mixed regression models, *p<0.05, Table S6-7 lists individual p values). (D) Pie charts depict relapse within

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30 days of medication wean for OP and ASMs (Fisher's exact, p<0.0001). For other immunotherapies, relapses occurred after the 30 day window. (E) Dot plot depicting the treatment durations prior to taper of OP or ASM (y-axis) in associaton with or without relapses (x-axis; ANOVA with multiple comparisons, p=0.37). ASM = anti-seizure medication, CD20 = B lymphocyte antigen 20, IVIG = intravenous immunoglobulin, IVMP = intravenous methylprednisolone, IT = immunotherapy, OP = oral prednisolone, PLEX = plasma exchange, SSA = steroid sparing agent.

Figure 4 Patient-rated favourable outcomes recalibrate mRS thresholds. (A) Dot plot depicting patient (left) or neurologist (right) perceived recovery rated 0-100% compared to premorbid function plotted against modified Rankin scale (mRS) at the latest clinical follow up (ANOVA with Dunn's correction for multiple comparisons, *p<0.05, exact p values shown in figure). From a total of 82 UK patients with QoL ratings, 69 had patient ratings and 74 neurologist ratings. (B) Patient vs neurologist rating correlations (Pearson r=0.85, n=63 patients). (C) Pie charts depicting typically both reported and revised favourable (green) and unfavourable (gray) outcomes (Chi-square test, *p<0.001), from 133 patients with mRS reported at one-year. mRS = modified Rankin Scale.

Figure 5 Influence of immunotherapy on favourable mRS outcomes. (A) Modified Rankin score (mRS) distributions at year 1 depicted for favourable (green) and unfavourable (gray) outcomes in patients either not exposed to immunotherapy (IT) compared to patients treated with IT (Mann-Whitney test, *p=0.03). Binary proportions of favourable and unfavourable outcomes for revised and reported mRS scores are depicted to the right (Fisher's exact, p=0.03 and p=0.99) (B) Multivariable analysis exploring how clinical and treatment features associate with odds ratio for a favourable outcome at 1 years (generalized mixed regression model, *p<0.05, exact p values shown for each variable, from a total of 130 patients), adjusted for treatment centre. Initial models did not adequately fit when treatments utilized in fewer patients (mycophenolate, azathioprine, tocilizumab, cyclophosphamide, methotrexate, cyclosporin, tacrolimus) were included as individual covariates. Thus, these were grouped as steroid sparing agents (SSA). (C) Sensitivity analysis of the primary model (B) demonstrating worsening ratio of a favourable outcome at 1 year based on time of initiation of immunotherapy. CD20 = B lymphocyte antigen 20, IVIG = intravenous immunoglobulin, IVMP = intravenous methylprednisolone, IT = immunotherapy, OP = oral prednisolone, PLEX = plasma exchange, mRS = modified Rankin Scale, SSA = steroid sparing agents

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Figure 6 Relapses associate with increased long-term disability. (A) Proportions of modified Rankin score (mRS) distributions based on monophasic or relapsing clinical course (left, Kruskal-Wallis test, *p=0.007, from n=174) with proportion of favourable (green) vs unfavourable (grey) outcomes (right, Fisher's exact, *p=0.03). (B) The mRS at clinical nadir (right) did not differ between groups (Kruskal-Wallis test, p=0.22). (C) Dot plot depicts each patient or neurologist perceived percentage of recovery rated from 0 – 100% following relapse, for 63 particpants with both patient and neurologist ratings available (two-sided Student's t test, *p=0.01 & p=0.03). (D-E) Proportions of mRS score distributions demonstrate significant worsening of mRS with increasing relapses (Kruskal-Wallis tests, p=0.005 and p=0.008), despite comparable mRS at nadir (Kruskal-Wallis test, p=0.28). (F) mRS score distrubtions for monophasic (left) and relapsing (right) clinical courses in patienst followed for 6-years. The area under the curve (AUC) for favourable outcomes (mRS 0-1) in monophasic patients is AUC=344, versus AUC=235 for relapsing patients (Fisher's exact, *p=0.047). mRS = modified Rankin Scale.

Figure 7 Treatment and Serological associations with clinical relapse and disability. (A) Pie charts depict proportions of clinical relapse follow exposure or no exposure to immunotherapy at the onset episode (IT, Fisher's exact *p=0.0002). (B) Hazard ratio and 95% confidence interval for future relapse following treatment exposure (Andersen-Gill survival model, *p<0.05, exact p values shown, n=141 total), after adjustment for concomitant antibodies and tumours. (C) Bar chart depicting the proportion of maintenance treatment medication exposures after which a decision was made to trial an additional first-line treatment rescue therapy for any reason. (D) Secondary exploration of the primary model (B) investigating the influence of oral prednisone wean on short-term (less than 30 days) relapse risk within 30 days of wean depicting hazards ratio and 95% confidence interval (Cox proportional hazards model, *p<0.05, exact p values shown). (E) Breakdown of relapse risk observed in (D) by the starting dose at which oral prednisolone was weaned (*p<0.05, exact p values shown). (F) Associations between LGI1-IgG levels and LGI1-IgM presence with mRS scores 0 – 1 (n=49; generalized mixed regression models, *p<0.05, exact p values shown) and (G) with relapse (n=40, Cox proportional hazards models, *p<0.05, exact p values shown). (H) After 1 year, presence of LGI1-IgM associated with a relapsing course (Fisher's exact, p=0.0007, odds ratio infinity); there was no association with LGI1-IgG (p=0.99). Overall, duration from immunotherapy exposure to serum sample was 138 days (range -53-1176). AZA = azathioprine, CD20 = B lymphocyte antigen 20, CYC = cyclophosphamide, IVIG = intravenous immunoglobulin, IVMP =

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intravenous methylprednisolone, LGI1 = leucine-rich glioma inactivated 1, MMF = mycophenolate mofetil, mRS = modified Rankin Scale, OP = oral prednisolone, PLEX = plasma exchange, SSA = steroid sparing agents, TOC = tocilizumab.

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Table 1 Demographics, clinical and paraclinical features, and immunotherapy exposures

	LGI1-Ab-E cohort n = 181
Demographics	
Onset age (years)	63 (23–92)
Male sex	122 (67.4%)
Ethnicity	
Caucasian	143 (79.0%)
Asian	35 (19.3%)
Hispanic	2 (1.1%)
African American	1 (0.6%)
Clinical Features	
Cognitive	168 (92.8%)
Seizures (any)	161 (89.0%)
FBDS	96 (53%)
Focal Seizures	141 (77.9%)
Behavioral	107 (59.1%)
Sleep	94 (51.9%)
Dysautonomia	41 (22.7%)
Neuropathic Pain	31 (17.1%)
Neuromyotonia	13 (7.2%)
Clinical Course	
Median nadir mRS (range)	3 (1–5)
Relapse	68 (37.6%)
Disease duration at latest follow up (years)	3.4 (0.3–14.9)
Paraclinical Features	
Hyponatremia	93/139 (66.9%)
Inflammatory CSF	55/128 (43.0%)
Abnormal EEG	101/145 (69.7%)
Abnormal MRI	95/169 (56.2%)
Immunotherapy exposures	
Oral prednisone	138 (76.2%)
Intravenous methylpredisone	113 (62.4%)
Intravenous immunoglobulins	85 (47.0%)
Rituximab	57 (31.5%)
Plasma exchange	51 (28.2%)
Mycophenolate	26 (14.4%)
Azathioprine	21 (11.6%)

Immunotherapies reported when administered to >20 patients (others shown in Figure 2). Denominators not shown when n=181. FBDS = faciobrachial dystonic seizures; LGI1-Ab-E = leucine-rich glioma-inactivated-1 antibody encephalitis; mRS = modified Rankin scale.

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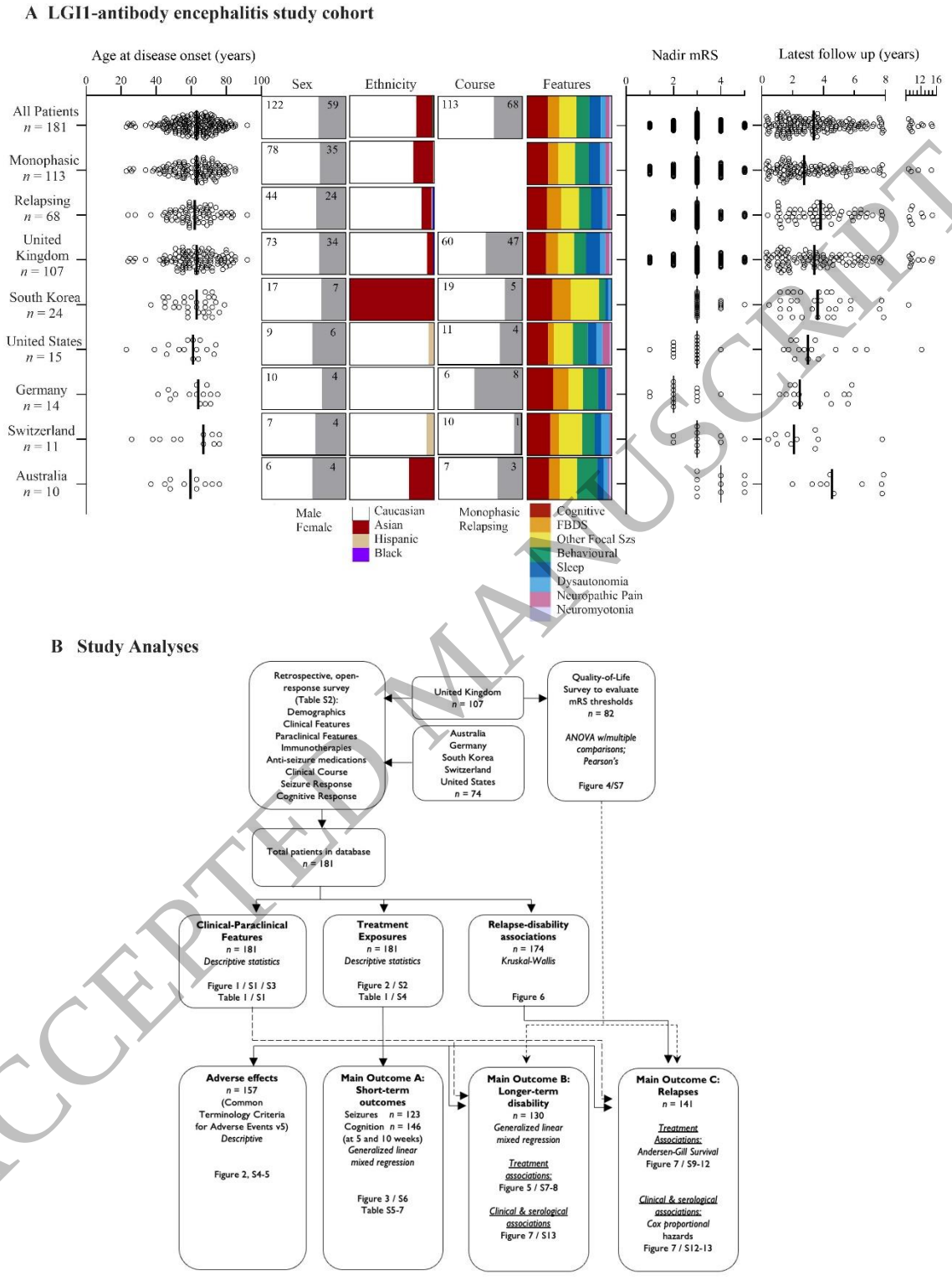


Figure 1
152x206 mm (x DPI)

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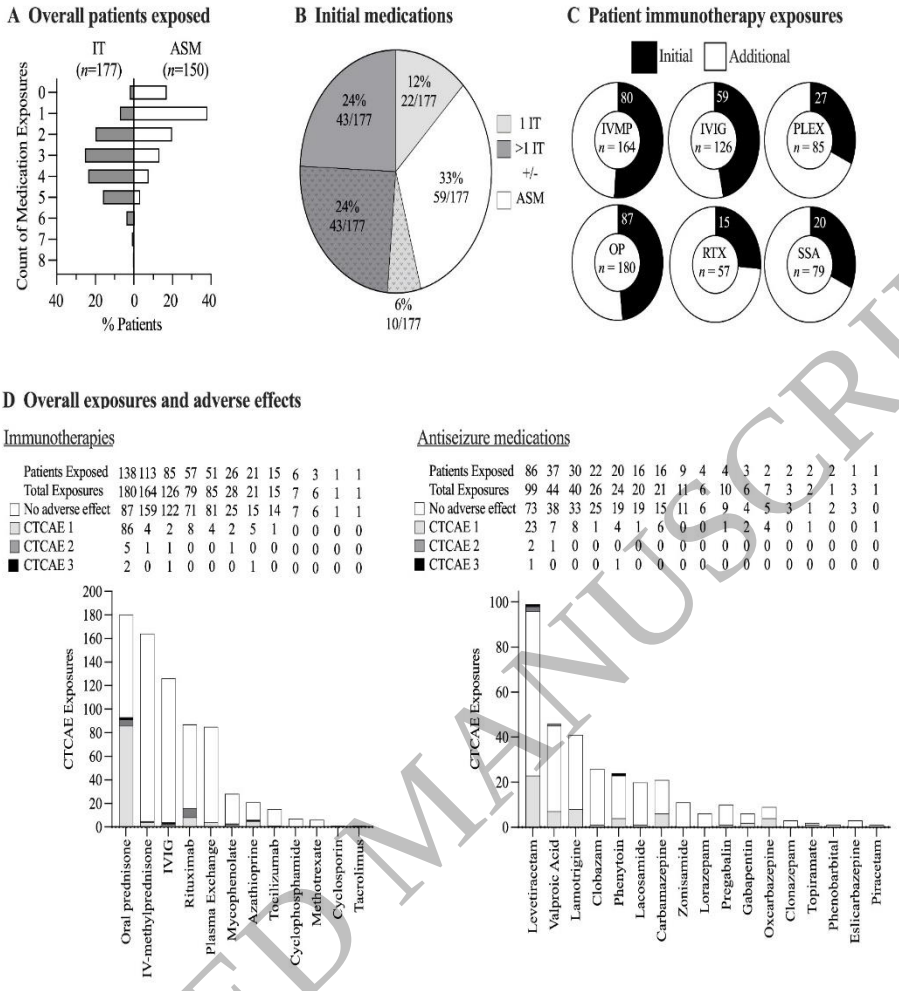


Figure 2
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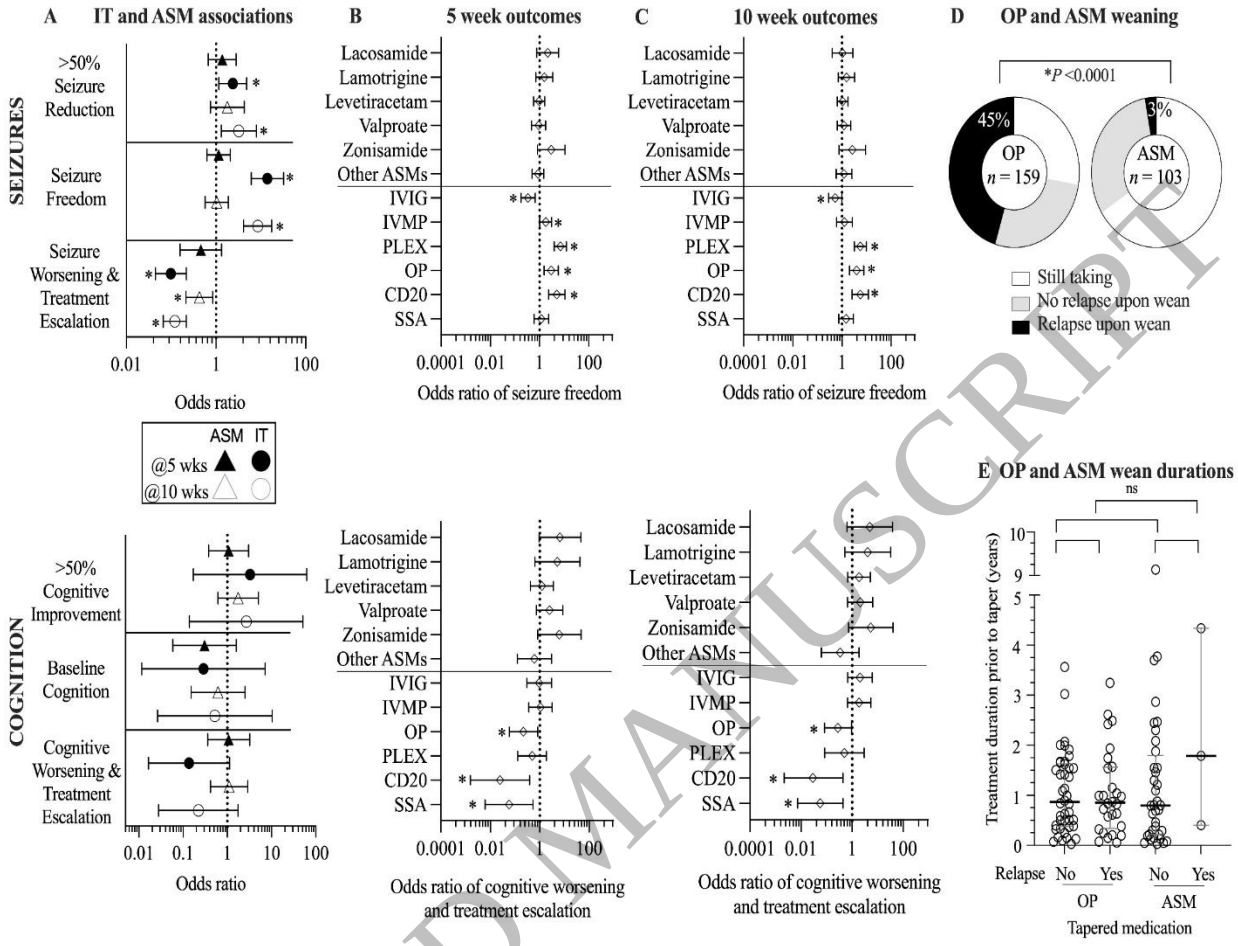


Figure 3
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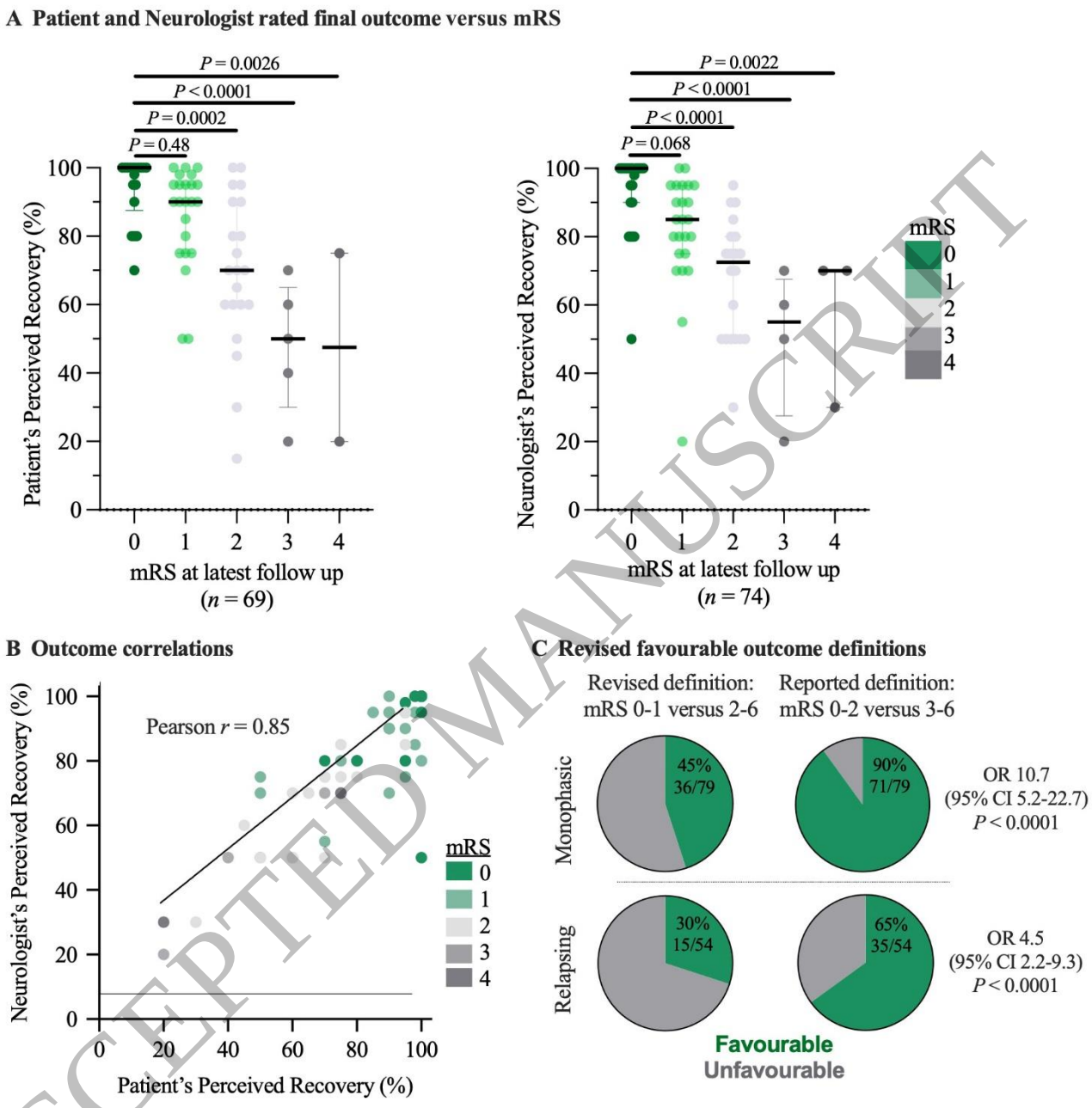


Figure 4
175x175 mm (x DPI)

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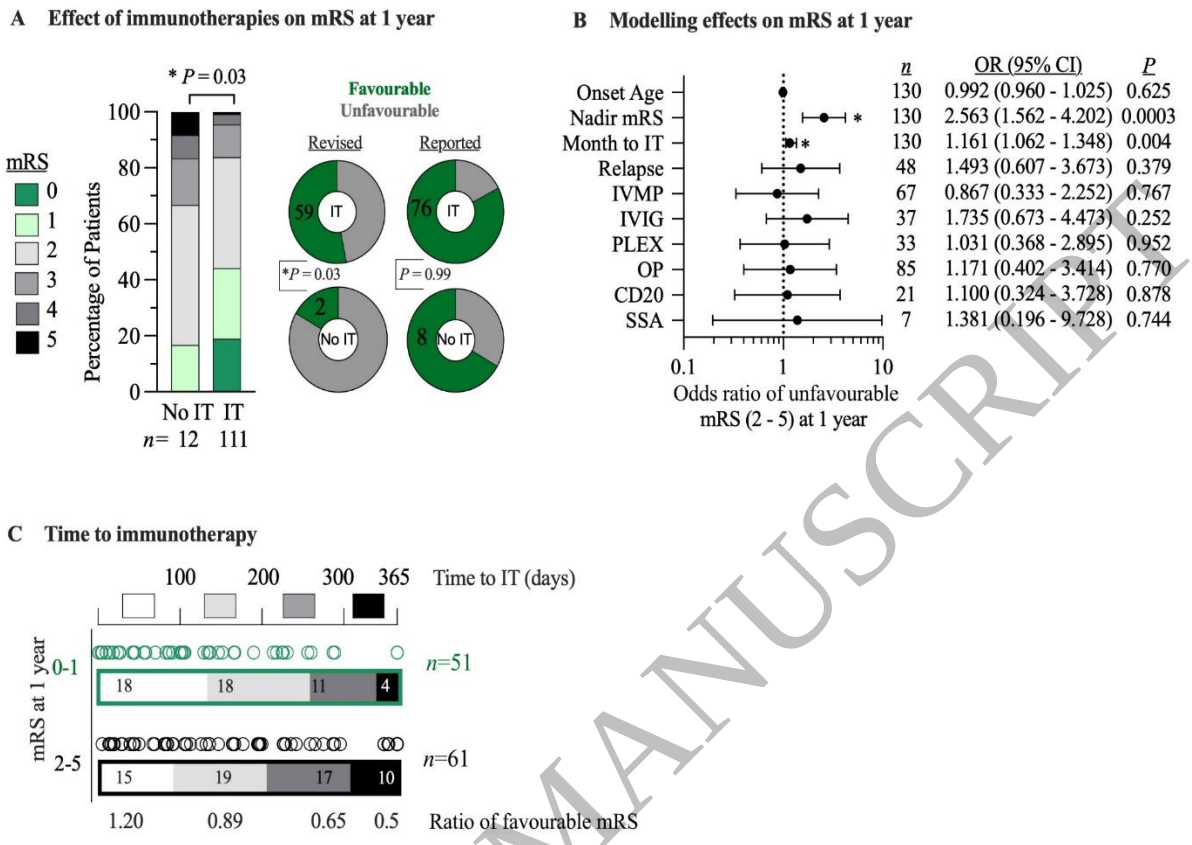


Figure 5
244x160 mm (x DPI)

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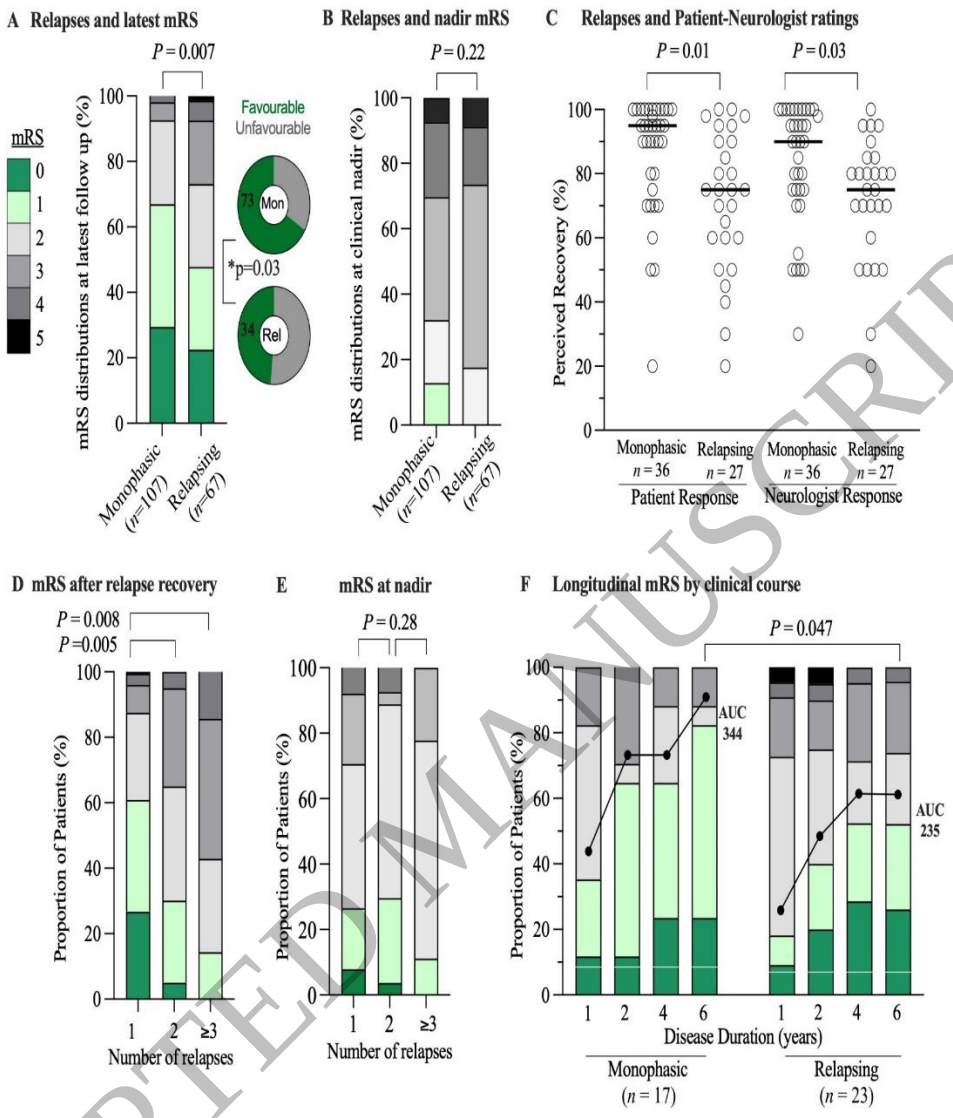


Figure 6
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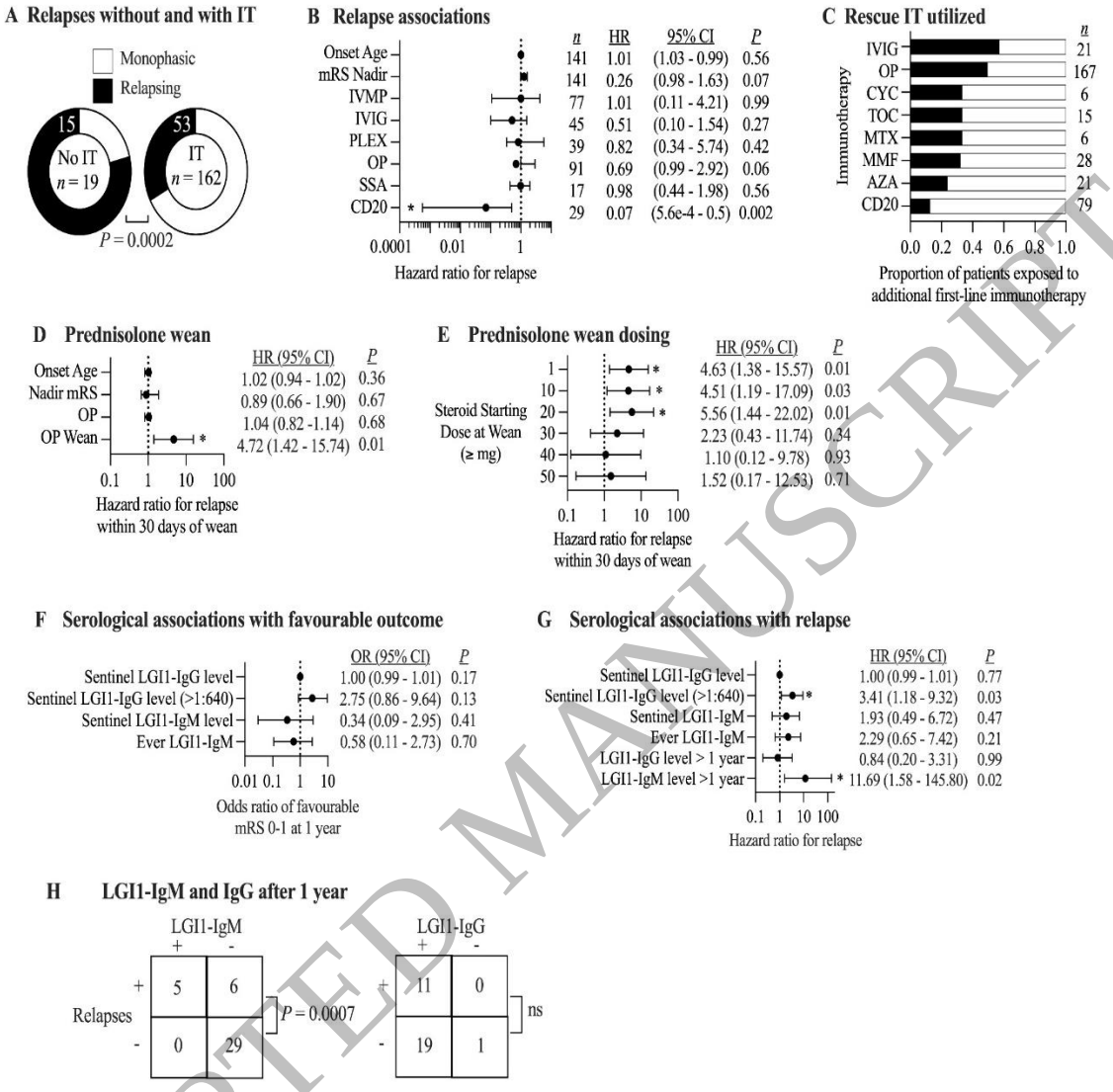


Figure 7
250x199 mm (x DPI)

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