Early Serum Galactomannan Trend as a Predictor of Outcome in Invasive Aspergillosis

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ABSTRACT

Monitoring and prediction of treatment response in invasive aspergillosis (IA) is difficult. We determined whether serum galactomannan index (GMI) trends early in the course of disease may be useful in predicting eventual clinical outcome. From the subjects recruited into the multicentre Global Aspergillosis Study, serial GMI were measured at baseline, and at Weeks 1, 2 and 4 following anti-fungal treatment. Clinical response and survival at 12 weeks were the outcome measures. GMI trends were analyzed using generalized estimating equations approach. GMI cut-offs were evaluated using receiver operating curve analysis incorporating pre- and post-test probabilities. From the 202 study patients diagnosed with IA, 71 (35.1%) had baseline GMI >0.5. Week 1 GMI was significantly lower in eventual responders to treatment at Week 12 as compared to the non-responders (GMI 0.62±0.12 versus 1.15±0.22 respectively, p=0.035). A GMI reduction >35% between baseline and Week 1 predicted probability of satisfactory clinical response. In IA patients with pre-treatment GMI <0.5 (n=131, 64.9%), GMI ought to remain low during treatment and a rising absolute GMI to >0.5 at Week 2 despite anti-fungals heralded poor clinical outcome. Here, every 0.1 unit increase in GMI between baseline and Week 2 increased the likelihood of unsatisfactory clinical response by 21.6% (p=0.018). In summary, clinical outcomes may be anticipated by charting early GMI trends during the first two weeks of anti-fungal therapy. These findings have significant implications for the management of IA.
BACKGROUND

Invasive aspergillosis (IA) remains the most common mould infection, causing significant mortality and morbidity in immunocompromised patients (16, 19). Securing a firm diagnosis of the disease and monitoring the response to treatment is difficult, as the patient may not exhibit reliable symptoms and signs in the presence of neutropenia and immune-modulating drugs, such as corticosteroids. Over the years the diagnostic capability for detection of IA has improved through the use of Aspergillus galactomannan antigen. Galactomannan (GM) from the Aspergillus cell wall is released during invasive disease and the level of circulating GM may be indicative of the intrinsic fungal burden in the host, at least in patients with underlying hematological malignancies or undergoing hematopoietic stem cell transplantations (HSCT) (13). GM can be detected by the Platelia Aspergillus enzyme immunoassay (PA-EIA; Bio-Rad Laboratories) and results are reported as the galactomannan index (GMI) (14, 23). GMI measurements have been studied extensively, gaining general acceptance as a non-invasive diagnostic tool for IA in at-risk patients (9), and have been included as a mycological criterion for case definition of probable IA by the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) consensus group (2, 7, 20).

Furthermore, in addition to serving as a diagnostic tool, serial GMI determination have been suggested to be useful for following treatment response (1), or used as a surrogate endpoint for outcome in invasive aspergillosis (8, 12, 15). However, the potential use of
GMI trends to predict eventual clinical outcomes early in the course of IA has not been well established, although it may have significant implications for patient management.

Herein we report findings from a study involving a cohort of 202 IA patients enrolled in a multicentre anti-fungal drug trial in which we assessed, retrospectively, whether serial serum GM trends early in the course of treatment correlated with the outcome of IA.
METHODS

Study Patients and Design

Patients had been enrolled in Study Protocol 150-307 performed in Europe, Israel and Australia under the aegis of the Invasive Fungal Infections Group of the European Organization for Research and Treatment of Cancer (EORTC). This and Study Protocol 150-602 comprised the Global Comparative Aspergillosis Study, a multicenter randomized trial that compared the efficacy of voriconazole versus amphotericin B deoxycholate for primary treatment of invasive aspergillosis. Selection of eligible patients for the trial, as well as the case definitions were as previously detailed (5). The protocol was approved by the appropriate institutional review boards, and written informed consent was obtained from all patients.

Outcome measures were originally assessed by an independent and blinded data review committee (DRC) based on reviews of clinical, mycological and systemically collected radiological data (5). Satisfactory clinical response was defined as a complete or partial response at week 12 after commencement of anti-fungal therapy; while poor response was defined as treatment failure or stable disease at the above pre-set endpoint, in accordance with the pre-established assessment criteria of the blinded DRC. The other definitive outcome measure was survival at 12 weeks after start of anti-fungal treatment.
Blood samples were obtained serially from trial patients at baseline prior to initiation of the designated study anti-fungal therapy and at intervals of weeks 1, 2 and 4 following initiation of treatment. The specimens were stored at -20°C prior to assay, multiple freeze thaw cycles were avoided. Serum GM was measured at a central laboratory (Health Protection Agency Mycology Reference Laboratory, Bristol, U.K.) within 7 – 12 months of the completion of the trial, and performed according to the manufacturer’s instructions (Platelia Aspergillus EIA, Bio-Rad Laboratories, Marne-la-Coquette, France). Results were recorded as the galactomannan index (GMI) which was relative to the optical density of the mean cut-off of the control sample obtained in the same run. Random testing for stability of the stored specimens over a maximum period of 13 months yielded an average GMI decrease of 11%. All reagents were obtained from Bio-Rad Laboratories. The GM results were not included in the primary analysis as the measurements were performed after efficacy and safety data had been published (5). For the purpose of this study, cases have been re-classified according to the 2008 EORTC/MSG criteria for invasive aspergillosis (2). Galactomannan results have been incorporated for this classification.

Statistical Analysis

Time profile of GMI or ΔGMI (GMI-change between 2 specified time points) for different outcomes at week 12 (based on clinical response and survival at week 12) were presented graphically, by plotting the mean per time point with the standard error of the mean (SEM). The generalized estimation equations (GEE) approach was used to test
and estimate changes in the effect size for GMI, accounting for repeated measurements overtime within patients and adjusting for the following covariates: age, sex, underlying hematological condition (leukemia/lymphoma versus hematopoietic stem cell transplantation), neutropenia and receipt of primary trial drug (amphotericin B versus voriconazole). Neutropenia was defined as a neutrophil count of less than 500 per cubic millimeter in the previous 2 weeks prior to recruitment into the trial. The Generalized Linear Model (GLM) using the binomial family and identity link function was used to estimate the risk differences in the magnitude of change of $\Delta GMI$, and to ascertain the differences in effect size in relation to the specified clinical outcome. The above covariates were factored in the regression analyses.

Results from the trend analysis using GEE were used to indicate which GMI study parameters might potentially be of use as predictive tool. The positive likelihood ratio (LHR) was used to assess the utility of GMI as a prognostic test. The conditional probability of LHR was calculated as $[(T^+C^+)/Total\ C^+] / [(T^+C^-)/Total\ C^-]$, where $T^+$=test positivity $T^+$, while $C^+$ or $C^-$ denote presence or absence of condition respectively (i.e. clinical response or survival by week 12) (3). A LHR > 1.0 was taken as a positive test to predict probability of designated condition/outcome. The receiver operating characteristics (ROC) analyses were performed against the selected GMI study parameter, which may either be absolute GMI values at the specified time point or based on the change of GMI between 2 specified time points i.e. $\Delta GMI$ to examine the predictive ability of different cutoff points for GMI values. The threshold for statistical
significance was set at p < 0.05 for aforementioned statistics.
RESULTS

Two hundred and two patients had a diagnosis of proven, probable or possible invasive aspergillosis, with at least two serum GMI results available for analysis. The patient demographics are presented in Table 1. Of these patients, 183 (90.6%) had invasive pulmonary aspergillosis. One hundred and fifty-three patients (75.7%) had underlying leukemia or lymphoma and were receiving chemotherapy; while another 39 (19.3%) were HSCT patients.

Serum galactomannan measurements were performed on 695 distinct serial specimens obtained at the respective study intervals: baseline (n=202), week 1 (n=179), week 2 (n=165) and week 4 (n=149) after initiation of anti-fungal therapy. Seventy-one of the 202 patients in the trial (35.1%) had a baseline GMI measurement of > 0.5.

Serial GMIs at baseline, weeks 1, 2 and 4 were assessed in relation to eventual clinical response and survival at week 12. The GMIs generally showed a downward trend with anti-Aspergillus treatment. Notably GMI trends of the proven/probable IA sub-cohort (n=147) were similar to the overall IA patient cohort of the original primary efficacy study (5) (consisting of proven, probable or possible IA cases, n=202, see Supplementary Data 1); and this larger cohort was employed for the intent of this study. In lieu of the Platelia Aspergillus EIA diagnostic cut-off which is currently established at 0.5 for test positivity (11), we studied the patients stratified as per baseline pre-treatment GMI > and
< 0.5 as it was observed that the GMI trends differed during the course of therapy as described below.

**GMI and Clinical Outcomes in Patients with Baseline GMI ≥ 0.5**

Of the 71 IA patients who had GMI ≥ 0.5 upon entry into the clinical trial, 29 (40.9%) patients had a satisfactory clinical response at week 12. The remaining 42 (57.1%) patients were assessed to have a poor response to therapy at end of study as determined by the DRC.

**Week 12 Clinical Response**

Non-responders at week 12 (W12 Non-responders) tended to have higher GMI (mean 1.44±0.22) at baseline than responders (mean GMI 1.16±0.22), but this difference was not significant (p=0.52). However, responders (W12 Responders) had a reduced week 1 GMI value compared to patients who eventually failed treatment (GMI 0.62±0.12 versus 1.15±0.22 respectively, p=0.003 by GEE analysis; Figure 1a). This difference remained statistically significant after adjustment for the co-variates: age, sex, neutropenia, underlying disease and primary trial drug (p=0.035 with multivariate GEE analysis).

The absolute GMI readout at week 1 was a suboptimal tool to predict clinical response at 12 weeks (AUC 0.41 through ROC analysis) despite this difference being statistically
significant on GMI profile analysis as above. The persistence of an absolute GMI > 0.5 at weeks 1 and 2 despite treatment was also not predictive of eventual clinical response (positive likelihood ratio, LHR not significantly >1, Figure 1a). On the other hand, through ROC analysis, the relative change in GMI from baseline to week 1 ($\Delta \text{GMI}_{\text{baseline} \rightarrow \text{W1}}$) was helpful in predicting W12 response to IA treatment. A reduction of GMI > 35% from baseline to week 1 yielded a LHR of 3.84 for W12 clinical response (AUC 0.72). In the context of this specific patient cohort, $\Delta \text{GMI}_{\text{baseline} \rightarrow \text{W1}}$ showing a reduction > 35% following commencement of IA treatment improved the post-hoc probability of clinical response at 12 weeks from 40.9% (at diagnosis of disease) to 72.7% (post-test probability).

**Week 12 Survival**

Forty-eight of these 71 patients (67.6%) with baseline GMI > 0.5 survived until the designated study end-point. However, GMI trends were non-discriminative between eventual survivors and non-survivors of this cohort (Figure 1b).

In summary, the above results suggest that for IA patients with a baseline GMI > 0.5, a significant drop of serial GMI levels during the early course of anti-fungal treatment is predictive of an eventual satisfactory clinical response. In our patients, a $\Delta \text{GMI}_{\text{baseline} \rightarrow \text{W1}}$ reduction of more than 35% increased the post-hoc probability of an eventual clinical response to treatment at 12 weeks.
GMI and Clinical Outcomes in Patients with Baseline GMI < 0.5

One hundred and thirty-one patients diagnosed with IA had a baseline GMI of less than 0.5 (2). Sixty-five of these (49.6%) had a satisfactory response at week 12 (Table 1). The survival rate was 74.1% in this cohort.

**Week 12 Clinical Response**

Baseline and week 1 absolute GMI values were similar in W12 responders and non-responders with pre-treatment GMI < 0.5, but notably, a distinct rise in GMI was seen in W12 non-responders by Week 2 (Figure 2a). Non-responding patients displayed a markedly increased $\Delta GMI_{baseline \rightarrow W2}$ ($p$ value was 0.001; by GEE univariate analysis and also after incorporating multivariate adjustment). Likewise, $\Delta GMI_{W1 \rightarrow W2}$ was significant ($p$ value 0.04 to 0.022 following multivariate adjustment).

An increase of absolute GMI to more than 0.5 after 2 weeks of treatment was associated with a trend towards an unsatisfactory treatment response (LHR 1.18-5.62, Figure 2a) although this was not statistically significant. Correlation of $\Delta GMI$ with W12 clinical response had a modest effect (AUC 0.59); a $\Delta GMI_{baseline \rightarrow W2}$ increase of 0.17 yielded a likelihood ratio of 4.19 for treatment failure at week 12. Using this cut-off in this cohort of patients, the post-hoc probability of treatment failure was increased from 50.4% (at commencement of therapy) to 81.0% (post-test probability) when $\Delta GMI_{baseline \rightarrow W2}$ increased by more than 0.17.
Week 12 Survival

Early GMI trends between W12 survivors and non-survivors mirrored that of treatment response (Figure 2b): increasing GMI trends by week 2 were predictive of mortality. After multivariate adjustments were made, the difference in GMI trends (ΔGMI_{baseline→W2} and ΔGMI_{W1→W2}) remained significant between survivors and non-survivors. The p values for both ΔGMI_{baseline→W2} and ΔGMI_{W1→W2} were both < 0.001 (following univariate and multivariate GEE analysis).

The above GMI trends relating to W12 survival were of prognostic value. A rising GMI value beyond 0.5 at 2 weeks despite appropriate treatment, was predictive of mortality by week 12 in IA patients whose pre-treatment GMI was <0.5 (LHR 4.48-11.00, Figure 2b). Furthermore, in applying ROC analysis for ΔGMI_{baseline→W2}, an increase of GMI > 0.13 yielded a likelihood ratio of 6.65 for eventual mortality by week 12 (AUC 0.70). Applying these values to this study cohort, patients experiencing an increase in GMI > 0.13 from baseline to week 2 had their post-test probability of W12 mortality increased 2.4 fold, from 25.9% (upon diagnosis of IA) to 69.9%.

Hence for an IA patient who started with a baseline GMI < 0.5, a rising absolute GMI to > 0.5 after 2 weeks despite treatment heralded a poor outcome. GLM analysis to estimate risk differences further concurred with the above findings and showed that among patients with baseline GMI <0.5, the every magnitude of increase in GMI from
baseline to week 2 ($\Delta GMI_{\text{baseline} \rightarrow W2}$) was associated with increased likelihood of unsatisfactory clinical response of 21.6% (95% confidence interval 19.4–23.8, p=0.018) at week 12.
Discussion

In the present study, using the well-characterized cohort of IA patients from the Global Aspergillosis Study, we have demonstrated that early serum GMI trends have prognostic value for clinical outcome. For IA patients starting treatment with baseline GMI ≥ 0.5, a progressive decline in GMI trends all through the first 4 weeks of therapy was reassuring; in particular, $\Delta \text{GMI}_{\text{baseline} \rightarrow W1}$ decline of >35% increased the probability of satisfactory clinical response. In patients fulfilling the diagnostic criteria for IA but with baseline GMI < 0.5, GMI values remaining low through first 4 weeks of treatment are anticipated for a satisfactory clinical response. However, in this latter subgroup, every 0.1 unit increase in GMI index between baseline and after 2 weeks of anti-fungal treatment ($\Delta \text{GMI}_{\text{baseline} \rightarrow W2}$) increased the likelihood of poor clinical response by 21.6%.

Clinical response to anti-fungal treatment in hematological patients with IA may be obscured in the presence of neutropenia, concurrent immunomodulatory drugs and the compromised immune system of the host. Until recently, assessment of response has been difficult in the absence of a reliable surrogate marker of the disease state (21). With the introduction of the Platelia Aspergillus GM EIA, much interest has been generated on the usefulness of the GM assay as a diagnostic tool for IA in various clinical settings (9, 10, 18, 22). However, the potential role of GM as a marker of disease status has been less studied and derived mostly in monocentric limited studies. This aspect was first explored by Boutboul et al who reported that increasing GMI levels were
associated with disease progression (1). It is only recently that two independent groups have reported findings that serum *Aspergillus* GMI correlates with IA outcome and could potentially serve as a surrogate disease marker. Using survival as a definitive outcome, Anaissie et al first noted that normalization of serum GMI (to < 0.5) after treatment was associated with survival (24). Similarly, Maertens et al have shown that normalization of GMI (to <0.5) 6 weeks after start of anti-fungal therapy correlated strongly with both response and survival (8). Subsequently, Anaissie et al performed a literature review of prior published studies and found that serial GMI trends through the course of illness showed a strong correlation with clinical outcome (15). Even more recently, the same group reported that GMI normalization was an early indicator for assessment of response (17).

Our findings here differ from the earlier observations made by the above latter two groups on three aspects.

Firstly, the design of the earlier studies stemmed from the original intent of using GMI as a surrogate end-point to assess outcome of therapy (12). As such, serial GMI measurements of IA patients were followed up until within eventual outcome as end-point (i.e. either discharge or death) by Anaissie et al (15, 24), or in the case of Maertens et al, the earliest assessment point was at 6 weeks post start of anti-fungal therapy (8). In the latest analysis by Anaissie et al, the study end-point was the degree of agreement and time to outcome between the EORTC/MSG criteria and GMI normalization. Here the
group found that time to GMI normalization in clinical responders was in the range of 15-41 days (median 21 days) after initiation of treatment (17). In our case, we intended to study early GMI trends as a potential tool to predict eventual clinical outcome. We were able to demonstrate that GMI trends as early as 1-2 weeks after start of appropriate antifungal therapy might be predictive of clinical outcome at 12 weeks.

Secondly, analyses of the earlier studies were performed using GMI as a dichotomous variable i.e. either positive > 0.5 or negative < 0.5. In our study design, we used GMI as a continuous variable and were able to (i) correlate increasing GMI with poor outcome/survival and (ii) quantitatively assign an early GMI reduction cut-off value as being associated with specified eventual clinical response at 12 weeks.

Thirdly, although the GM assay has, to date, been acknowledged as a reliable means to assist the diagnosis of IA (9, 18), we recognize that at the bedside, not all patients with a high suspicion for IA on clinical grounds will fulfill all the EORTC diagnostic criteria (including having a GMI > 0.5) (2). At-risk patients with a strong clinical suspicion of IA, but with GMI of < 0.5 nonetheless, will still be initiated on anti-Aspergillus therapy by their attending physicians. With our well-characterized cohort of IA patients, we were able to stratify the patients into those with baseline GMI < or > 0.5. By following their respective GMI profiles, we also showed that the GMI trends during the course of illness differed between IA patients with starting GMI < or > 0.5.
Our findings here do at first sight, seem analogous to those of Koo et al (6) which recently reported that the GMI trend between baseline and week 1 was predictive of mortality at 6 weeks in 74 GM-positive (>0.5) IA patients. However, in our patients with baseline GMI > 0.5, the early GMI trend had only a modest prognostic value for clinical outcome than had been anticipated. On the other hand, in the sub-cohort of IA patients with pre-treatment GMI < 0.5, a rising GMI > 0.5 by week 2 was linked to adverse outcomes. In addition we also derived early ΔGMI cut-off thresholds which were predictive of subsequent adverse clinical outcomes. The use of such simple prediction rules for the clinician at the bedside could enable timely identification of patients who may potentially fail first-line anti-fungal treatment, so as to facilitate intervention with more aggressive second line or combination anti-fungal therapy.

Invasive aspergillosis remains an invariably complex disease often requiring a protracted treatment course over months. Treatment response over time is determined by a conglomerate of dynamically changing factors, including the status of the primary hematological condition, reconstitution of host immune response, subsequent development of graft-versus-host disease as well as occurrence of other opportunistic infections, and the institution of concurrent immunosuppressive medication. It is presumptuous, to anticipate that early GMI trends over just the first 2 weeks of disease could act as the sole over-riding prognosticator of eventual clinical outcome weeks later. Yet our study reveals that initial GMI trends in selected patient cohorts have the propensity to predict not only treatment response, but also subsequent mortality. This
finding undoubtedly improves our capability to anticipate adverse outcomes in a difficult-to-treat disease, in which follow-up of treatment response is also challenging. Nonetheless it is hoped that as more is known of the pathophysiology of IA, other novel biomarkers and mitigating factors may be incorporated to further improve the current prediction model based on GMI trends.

The robust design of the Global Comparative Aspergillosis Study as well as the sizable patient numbers are pivotal in reinforcing the findings of this study. In our subjects, 35.1% had a positive GMI of $> 0.5$ at diagnosis of IA. Even in patients with proven and probable IA, GMI positivity was only 48.3%. The accuracy of the GM assay here was lower than reported by others in the literature (7, 20). Observations of similarly low GM positivity rates have also been reported in other major centers (4). This unique setting had also permitted us to profile the GMI trends of the 2 cohorts (starting GMI $< 0.5$) appropriately. Nonetheless, we acknowledge that the derived prediction capability of GMI is specific to the patient cohort in this study and may be subject to influence by the lower GMI positive prevalence rates here. Of note, we have also performed similar analysis of GMI trends on patients with just proven and probable IA in this cohort (n=147) and obtained similar results to those above. Whilst being a retrospective analysis, the strength of this study lies in that it utilizes the largest cohort of IA patients involved in a major, well-conducted, multi-centre clinical trial where the case definitions, end points and criteria for determination of clinical response were well-established and objectively determined by a blinded panel of experts.
In conclusion, we have shown that early GMI trends can be used to help predict eventual clinical response and mortality in patients with IA. Early identification of patients who may potentially fail therapy is crucial for facilitating prompt intervention and optimizing outcome in invasive aspergillosis.
Acknowledgement

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Conflict of Interest Disclosure

The original study protocols 150-307 and 150-602 were sponsored by Pfizer.

L.C. has received grant support from Pfizer and Merck Sharp and Dohme (MSD), and been an advisor/consultant for Pfizer and MSD.

B.J.K. has received grant support, has been an advisor/consultant and on the speakers’ bureau for Pfizer.

E.J. received funding from Pfizer for a voriconazole reference laboratory to measure fungal MICs and GMI levels. E.J. has served as consultant and member of the speaker’s bureau for Astellas, Gilead Sciences, MSD, Pfizer, Schering-Plough, and Zeneus (Cephalon).

J.M. has served as consultant to Schering-Plough, Gilead Sciences, Merck, Sharp & Dohme, Pfizer Inc., Bio-Rad, Fujisawa healthcare, Inc., Astellas, Nextar and Zeneus (Cephalon). J.M. has received research funding from Bio-Rad, MSD and Pfizer Inc. and been on the speaker’s bureau for Schering-Plough, Gilead Sciences, MSD, Pfizer Inc., Bio-Rad, Fujisawa healthcare, Inc, Astellas and Zeneus (Cephalon).
O.L. has been consultant and/or on the speakers’ bureau for Astellas, Gilead Sciences, Pfizer and MSD.

R.H. has been advisor/consultant and/or on the speakers’ bureau for Astellas, Basilea, Gilead, Pfizer and MSD.

H.T.S is an employee of Pfizer and P.F.T was previously an employee of and currently serves as an advisor to Pfizer. Both were not involved during the stage of result analysis for this study.

All other authors: no competing financial interest
Table 1. Demographic characteristics of study cohort and the treatment-related outcomes of interest. HSCT: hematopoietic stem cell transplantation. Week 12 Response: Clinical response at Week 12 as assessed by data review committee (DRC).

Figure 1. Galactomannan index (GMI) of patients with positive GMI $\geq 0.5$ at baseline plotted against pre-defined clinical outcome parameters at week 12: treatment response (a) or survival (b). # is the p value for the difference in absolute GMI value between W12 responders and non-responders. # p value was 0.003 by univariate analysis, after multivariate correction for age, sex, underlying hematological condition, neutropenia and receipt of primary trial drug (amphotericin B or voriconazole), # p value was 0.035. The number of distinct specimens analyzed at each time point is follow: Baseline (n=71), Week 1 (n=60), Week 2 (n=53) and Week 4 (n=42). Statistical analysis was performed by the generalized estimating equation (GEE) approach. The table below each graph depicts positive likelihood ratio (LHR) and 95% confidence interval (95% C.I.) of respective adverse outcomes (poor clinical response or mortality at week 12) should the GM index remain higher than the cut-off value as indicated.

Figure 2. Galactomannan index (GMI) of patients with baseline GMI $< 0.5$ at baseline plotted against pre-defined clinical outcome parameters at week 12: treatment response (a) or survival (b). The value enclosed by horizontal brackets represents multivariate p
value for the difference in $\Delta \text{GMI}$ of both groups between the indicated study interval, incorporating correction for age, sex, underlying hematological condition, neutropenia and receipt of primary trial drug (amphotericin B or voriconazole). The number of distinct specimens analyzed at each time point is follow: Baseline ($n=131$), Week 1 ($n=119$), Week 2 ($n=112$) and Week 4 ($n=102$). Statistical analysis was performed by the generalized estimating equation (GEE) approach. The table below each graph depicts positive likelihood ratio (LHR) and 95% confidence interval (95% C.I.) of respective adverse outcomes (poor clinical response or mortality at week 12) should the GM index remain higher than the cut-off value as indicated.
References


### Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 202)</th>
<th>p values</th>
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<tbody>
<tr>
<td></td>
<td>Baseline GMI &gt; 0.5</td>
<td>Baseline GMI &lt; 0.5</td>
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<td></td>
<td>n = 71 (%)</td>
<td>n = 131 (%)</td>
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<td><strong>Sex</strong></td>
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<td>Female</td>
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<td><strong>Certainty of Disease</strong></td>
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<td>Proven IA</td>
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<td><strong>Underlying diseases</strong></td>
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<td>Leukaemia/Lymphoma</td>
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<td>24 (19.0)</td>
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<td>63 (48.1)</td>
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<td>Amphotericin B</td>
<td>31 (43.7)</td>
<td>68 (51.9)</td>
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<td><strong>Week 12</strong></td>
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<td>Non-responders</td>
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<td>Survivors</td>
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<td>Non-survivors</td>
<td>23 (32.4)</td>
<td>34 (25.9)</td>
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</table>
(a) GM Index

<table>
<thead>
<tr>
<th>GM Cut-Off</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LHR</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>0.5</td>
<td>1.04</td>
<td>(0.64-1.71)</td>
</tr>
<tr>
<td>0.6</td>
<td>1.13</td>
<td>(0.58-2.22)</td>
</tr>
<tr>
<td>0.7</td>
<td>1.41</td>
<td>(0.67-2.96)</td>
</tr>
<tr>
<td>0.8</td>
<td>1.27</td>
<td>(0.59-2.75)</td>
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</tbody>
</table>

# p=0.035

(b) GM Index

<table>
<thead>
<tr>
<th>GM Cut-Off</th>
<th>Week 1</th>
<th>Week 2</th>
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<tbody>
<tr>
<td></td>
<td>LHR</td>
<td>95% C.I.</td>
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<tr>
<td>0.5</td>
<td>0.92</td>
<td>(0.55-1.54)</td>
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<tr>
<td>0.6</td>
<td>0.93</td>
<td>(0.48-1.6)</td>
</tr>
<tr>
<td>0.7</td>
<td>1.04</td>
<td>(0.53-2.05)</td>
</tr>
<tr>
<td>0.8</td>
<td>0.95</td>
<td>(0.44-2.01)</td>
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</tbody>
</table>
(a) GM Index

<table>
<thead>
<tr>
<th>GM Cut-Off</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LHR</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>0.5</td>
<td>0.79 (0.32-1.99)</td>
<td>1.18 (0.51-2.74)</td>
</tr>
<tr>
<td>0.6</td>
<td>0.62 (0.2-1.87)</td>
<td>2.1 (0.63-7.01)</td>
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<tr>
<td>0.7</td>
<td>0.46 (0.05-4.3)</td>
<td>3.51 (0.72-17.24)</td>
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<tr>
<td>0.8</td>
<td>1.39 (0.09-21.57)</td>
<td>5.62 (0.65-48.59)</td>
</tr>
</tbody>
</table>

(b) GM Index

<table>
<thead>
<tr>
<th>GM Cut-Off</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LHR</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>0.5</td>
<td>1.57 (0.71-3.46)</td>
<td>4.48 (2.3-8.71)</td>
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<tr>
<td>0.6</td>
<td>1.08 (0.38-3.09)</td>
<td>6.6 (2.43-17.86)</td>
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<tr>
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<td>0.81 (0.09-1.08)</td>
<td>9.78 (2.81-34.05)</td>
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<tr>
<td>0.8</td>
<td>1.63 (0.15-17.26)</td>
<td>11 (2.37-51.07)</td>
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</tbody>
</table>