International Journal of Infectious Diseases 163 (2026) 108272

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Sequential serum galactomannan as outcome marker for invasive aspergillosis—An exploratory study from the FungiScope registry

Christina Többen[1,2,3], Oliver A. Cornely[1,2,3], Carolin S. Joisten[1,2,3], Ertan Sal[1,2], José A. Cozzi[4], Baptiste Hoellinger[5], Deniz Yilmaz Karapinar[6], Daniel Richter[7], Andreas H. Groll[8], Gustavo-Adolfo Méndez[9,10], Jeffrey D. Jenks[11,12], Nurettin Erben[13], Leyre López Soria[14], Philipp Koehler[1,2,15], Anna Apostolopoulou[16], Dries Deeren[17], Rika Draenert[18], Iker Falces-Romero[19], Julio Maquera-Afaray[20], Lisa Meintker[21], Ruwanthi Kolamunnage-Dona[22], Danila Seidel[1,2,#], Jannik Stemler[1,2,3,#,*]

[1] *Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, North Rhine-Westphalia, Germany*
[2] *University of Cologne, Faculty of Medicine and University Hospital Cologne, Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, North Rhine-Westphalia, Germany*
[3] *German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, North Rhine-Westphalia, Germany*
[4] *Centro de Referencia de Micología, F.C.B.F-UNR, Universidad Nacional de Rosario, Rosario, Argentina*
[5] *Department of Infectious Diseases, Strasbourg University Hospitals, Strasbourg, France*
[6] *Department of Pediatric Hematology, Ege University Medical School, Children's Hospital, Bornova, Izmir, Turkey*
[7] *Department of Anesthesiology, Heidelberg University Hospital, Heidelberg, Germany*
[8] *Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology and Oncology, University Children's Hospital Muenster, Muenster, Germany*
[9] *Infectious Diseases Service, Hospital Escuela de Agudos Dr. Ramón Madariaga, Posadas, Misiones, Argentina*
[10] *Infectious Diseases Department, Facultad de Medicina Universidad Católica de las Misiones, Posadas, Misiones, Argentina*
[11] *Durham County Department of Public Health, Durham, North Carolina, USA*
[12] *Division of Infectious Diseases, Department of Medicine, Duke University, Durham, North Carolina, USA*
[13] *Department of Infectious Diseases and Clinical Microbiology, Eskisehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey*
[14] *Clinical Microbiology Department, Hospital Universitario Cruces, Barakaldo, Spain*
[15] *Department I of Internal Medicine, Division of Clinical Immunology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, North Rhine-Westphalia, Germany*
[16] *Division of Infectious Diseases, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, New York, USA*
[17] *AZ Delta Hospital, Roeselare, Belgium*
[18] *Stabsstelle Antibiotic Stewardship, LMU Klinikum, Munich, Germany*
[19] *Clinical Microbiology and Parasitology Department, Hospital Universitario La Paz, Madrid, Spain*
[20] *Instituto Nacional de Salud del Niño San Borja, Lima, Perú*
[21] *Department of Internal Medicine 5, Hematology and Internal Oncology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Bayern, Germany*
[22] *Department of Health Data Science, University of Liverpool, Liverpool, UK*

ARTICLE INFO

Article history:
Received 6 September 2025
Revised 27 November 2025
Accepted 28 November 2025

Keywords:
Biomarker
Immunocompromised host
Treatment monitoring
Registry study
Invasive aspergillosis
Galactomannan assay

ABSTRACT

Background: Galactomannan index (GMI) is established as a diagnostic tool for invasive aspergillosis (IA), while its utility in monitoring antifungal treatment (AFT) response and prognostic value remains unclear. This study evaluated the validity of serum GM as a biomarker for AFT monitoring and its prognostic significance by correlating GMI with clinical response and survival of IA.

Objectives: Patients with IA and at least two sequential serum GMI measurements were identified from the FungiScope registry. Joint models of event-time and longitudinal outcome were used for imputing missing GMI to account for the relationship between GMI and time to death, as well as GMI and time to drop-out for the survival analysis and AFT response analysis, respectively. Cox proportional hazards models and logistic regression models assessed survival and clinical response on GMI changes at day 7, with baseline log GMI as an adjustment covariate.

* Corresponding author: Jannik Stemler, Department 1 for Internal Medicine and CECAD Institute of Translational Research, FECMM, University Hospital of Cologne, Kerpener Str. 62, Cologne, North Rhine-Westphalia 50937, Germany.
E-mail address: Jannik.stemler@uk-koeln.de (J. Stemler).
# These authors share senior authorship.

https://doi.org/10.1016/j.ijid.2025.108272

Results: Among 66 patients with IA, correlation between day 7 GMI predictions and observed values was 92% and 88% in the survival and AFT analysis, respectively. GMI decreased in both patients who died within 42 days and those who survived, but maintained higher in patients who died. GMI increased or declined less in patients who died within 42 days, whereas in survivors, a continuous decline of GMI was observed. Patients with a baseline GMI < 1 had a higher survival rate until day 42 (17/21, 81.0%) compared to those with GMI ≥ 1 (31/45, 68.9%), with a risk of death twice as high as with GMI < 1 (HR $= 2.107$, $P = 0.19$).

Conclusion: Serum GMI is a non-invasive, predictive tool for estimating survival probability at onset of IA. Early GMI changes correlate with survival and could prompt timely AFT adjustment, potentially improving clinical outcomes. Additionally, GMI could serve as surrogate endpoint in clinical trials, facilitating development of new antifungal strategies.

Introduction

Diagnosis of invasive aspergillosis (IA) is challenging and requires a combination of clinical, radiological, and microbiological data [1]. Timely antifungal therapy is crucial for the outcome of this life-threatening disease. While conventional microbiological and histopathological diagnosis is time-consuming, galactomannan (GM) detection in fluids is rapidly available with higher sensitivity [2]. GM is a polysaccharide of the *Aspergillus* cell wall and is released continuously during hyphal extension and tissue invasion, whereby its circulating level generally correlates with fungal biomass [3]. GM can be detected in serum, bronchoalveolar lavage fluid, and cerebrospinal fluid and has been established as a biomarker for early diagnosis of IA in immunocompromised patients [3]. Screening for GM in high-risk patients may increase the diagnostic yield and allow early diagnosis of IA value [3].

To guide therapeutic interventions and eventually improve patient outcomes, it is essential to identify patients with high probability of poor outcome of IA early [4]. Measuring GM index (GMI) serially may be suitable for monitoring treatment responses in patients with IA [4]. Although its prognostic value has not been widely acknowledged, GMI trends show a strong association and concordance with the clinical outcome [5]. However, the dynamics of GMI both at baseline and during therapy, including the extent of its decline and its relationship to clinical outcomes in patients, are yet to be systematically characterized.

The aim of this study was to assess the validity of serum GMI to monitor response to antifungal treatment (AFT) as well as its prognostic value by determining the relationship between the GMI and clinical response during the treatment of IA outside of a clinical trial setting, in a heterogeneous patient population with IA from the international FungiScope registry.

Methods

Data collection and data analysis

Clinical cases were collected in the FungiScope registry, a global web-based registry of invasive fungal infections [6]. FungiScope is a working group of the International Society for Human and Animal Mycology (ISHAM) and the European Confederation of Medical Mycology (ECMM). Clinical data were collected retrospectively via an online questionnaire hosted on www.clinicalsurveys.net (EFS Leadership 7.0 Version 1.2, Tivian XI GmbH, Cologne, Germany). All cases were validated by infectious diseases specialists to confirm eligibility for the analysis.

Patients with IA and at least two sequential serum GMI measurements during diagnosis, treatment, and follow-up were identified from the registry. The following data items were collected: demographic information, including age category and sex; risk factors and underlying conditions; diagnostic results, encompassing imaging and mycological data; affected organs and clinical patterns of the disease; details of AFT, including drug levels via therapeutic drug monitoring, if available; GMI results during diagnosis, treatment, and follow-up; as well as treatment response and survival. Antifungal susceptibility testing, including azole resistance, is documented in the registry; however, it is not a mandatory data collection item and can only be analyzed when available. Treatment response was assessed at days 28, 42, 84, and at the last available assessment. Day 0 was defined as the day on which the treating physician was first informed about a positive result from a microbiologist/pathologist confirming the diagnosis of IA.

Participants/inclusion criteria

Sequential serum GMI with an initial positive baseline result (optical density $\geq$0.5) were collected whenever at least two measurements were available during diagnosis, treatment, and follow-up. European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2020 criteria for probable/proven IA were applied [7], but we chose to modify these criteria by also including patients with GMI $\geq$ 0.5 and $<$0.7 without further mycological evidence in patients treated for clinically suspected IA [8]. Cases of coinfections with other molds than *Aspergillus*, cases of influenza-associated pulmonary aspergillosis, COVID-19-associated pulmonary aspergillosis, and cases published elsewhere were excluded.

Statistical methods

Data was analyzed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 30 (IBM Corp., Armonk, NY, USA) and was described employing frequencies and percentages, and median, range, and IQR as appropriate. Kruskal–Wallis test and Fisher's exact test were used to compare categorical data where appropriate. Cumulative mortality rates were calculated. *P*-values $\leq$0.05 were considered statistically significant. Interval-censored GMI values were imputed using deterministic methods to ensure completeness of the dataset.

GMI vs survival analysis

A Cox proportional hazards model was used to regress the survival on GMI changes from baseline to day 7, and another one with baseline log GMI as covariate. Survival was censored at 42 days to model the mortality in a short-term manner.

Since GM samples were taken whenever available in a real-world analysis manner, a joint event-time and longitudinal outcome model between GMI and time to death was used for imputing missing GMI for the analysis of GMI vs survival.

The following model was assumed:

- Longitudinal model: $\log(GMI_t(t) + 0.001) = \beta_0 + \beta_1 t + U_{0t} + U_{1t}t + U_{2t}t^2 + \varepsilon_t(t)$
- Survival model: $(t) = \lambda_0(t)\exp(\gamma_0(U_{0t} + U_{1t}t + U_{2t}t^2))$

Where γ_0 is the association parameter between the longitudinal and survival submodels, and the longitudinal submodel influences the hazard of the survival submodel via the shared random effects U_{0t}, U_{1t}, and U_{2t}.

We correlated day 7 GMI predictions with the actual GMI values, where available, to then compare the predicted GMI mean profile between patients who were alive vs deceased by day 42. Additionally, we compared the distribution of GMI change from baseline to day 7 between patients who were alive vs deceased by day 42.

A receiver operating characteristic (ROC) curve was produced to assess the ability of GMI change from baseline to day 7 to predict the survival status at day 42.

A Kaplan–Meier survival analysis compared time to death between patients with a baseline GMI $\geq$ 1 and those with baseline GMI $<$ 1.

GMI vs clinical response analysis

To evaluate serum GMI as a marker for treatment response in IA, a logistic regression model was used to assess if the GMI changes from baseline to day 7, as well as baseline log-transformed GMI, were associated with treatment response at day 84.

To address missing GMI values during follow-up, a joint model was used linking longitudinal GMI measures and time to dropout, whereby dropout was defined as the absence of response assessment at day 84. Patients with the final overall response assessment before day 84 were considered dropout (event), and those with data at day 84 or beyond were censored (no event).

With the joint model, we imputed predicted GMI values at day 7 and correlated these with the observed GMI values, where available, to then compare the predicted GMI mean profile between patients with treatment success vs failed treatment at day 84.

Finally, we compared the distribution of observed GMI changes from baseline to day 7 between the patients with treatment success vs failure, and another one with baseline log GMI as a covariate.

We generated a ROC curve to assess the predictive value of early GMI change for day 84 clinical response.

Explorative analyses

As an explorative analysis, we compared first-week treatment groups (azoles, polyenes, echinocandins; monotherapy vs combination treatment) with GMI mean profiles from the joint model for the overall population. The first-week treatment group was also included as a covariate in the Cox model and logistic regression model.

To explore further the association of neutropenia on outcome and GMI levels, we performed analyses comparing patients with a neutrophil count $<$ 100/µL vs those with $\geq$ 100/µL at the time of diagnosis of IA. For the comparison of those two groups, we used Fisher's exact test for qualitative variables and Kruskal–Wallis test for quantitative variables as a non-parametric test.

Results

Baseline characteristics

We identified 66 patients with IA in the FungiScope registry who were reported from Germany (n = 30, with 20 consecutive IA cases diagnosed between 2015 and 2024 from the University Hospital of Cologne, Germany), France (n = 11), Argentina (n = 10), Turkey (n = 8), Spain (n = 4), Peru (n = 2), and Belgium (n = 1) (Figure 1). The most frequently identified species was *Aspergillus fumigatus* (n = 23), followed by *Aspergillus flavus* (n = 8) and *Aspergillus terreus* (n = 2) (Figure 2). In 33 patients, the diagnosis was made from GM only without culture or histopathological identification. All patients had pulmonary IA, while eight patients had extrapulmonary involvement or disseminated infection (Table 1).

Table 1
Demographics and baseline characteristics of 66 patients with invasive aspergillosis.

	n = 66	%
Age		
1-6 years	8	12.1
7-11 years	2	3.0
12-16 years	2	3.0
17-29 years	9	13.6
30-49 years	12	18.2
50-69 years	27	40.9
70-89 years	6	9.1
Biological sex		
Male	40	60.6
Female	26	39.4
EORTC/MSG criteria		
Proven	10	15.2
Probable	51	77.3
Possible	4	6.1
Other[a]	1	1.5
Site(s) of infection		
Lung	58	87.9
Lung + paranasal sinuses	4	6.1
Lung + brain	2	3.0
Other[b]	2	3.0
Underlying conditions and host factors		
Haematological or oncological disease[c]	51	77.3
Allogenic HSCT	9	13.6
Autologous HSCT	5	7.6
Solid organ transplantation[d]	13	19.7
Active acute GvHD	3	4.5
Diabetes mellitus	6	9.1
Neutropenia	38	57.6
Corticosteroids	45	68.2
Other[e]	65	98.5
Antifungal treatment day 0-day 7[f]		
Antifungal prophylaxis[g]	18	27.3
Survival	27	40.9
Total GM measurements n = 413		
GM measurements per patient n = 5 (range 2-8)		
Baseline serum GMI: median, IQR: 1.280, 1.702		

GMI, galactomannan index; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; IQR, interquartile range.

[a] Patients were classified as proven (n = 10), probable (n = 51), or possible (n = 4) according to the revised 2020 EORTC/MSG criteria [8], as well as not classifiable under these criteria (n = 1).

[b] Lung, mediastinum (n = 1); lung, brain, mediastinum, ascending aorta (n = 1).

[c] Acute leukaemia (n = 27); aplastic anemia (n = 4); lymphoma (n = 9); myelodysplastic syndrome (n = 1); multiple myeloma (n = 3); Fanconi anemia (n = 1); solid tumor (n = 5); monoclonal gammopathy (n = 1).

[d] Liver (n = 2); heart (n = 8); liver, heart (n = 1); kidney, heart (n = 1); kidney (n = 1).

[e] Crohn's disease (n = 1); autoimmune neutropenia (n = 1); alcoholism (n = 1); chronic cardiovascular disease (n = 14); chronic liver disease (n = 2); chronic pulmonary disease (n = 6); chronic kidney disease or acute kidney injury (n = 7); obesity (n = 5); underweight (n = 1); viral pneumonia within 90 days prior invasive fungal infection (n = 7); treatment in ICU (n = 20).

[f] Azoles (n = 38); polyenes (n = 13); echinocandins (n = 3); azoles + polyenes (n = 6); azoles + echinocandins (n = 1); azoles + polyenes + echinocandins (n = 2); unknown (n = 3).

[g] Amphotericin B liposomal (n = 3); caspofungin (n = 2); fluconazole (n = 3); micafungin (n = 2); posaconazole (n = 5); voriconazole (n = 3).

GMI change from baseline vs survival

In the 66 patients, 413 GM serum measurements were available with a median of five per patient (range 2-8). Platelia *Aspergillus* assay (Bio-Rad) was used to detect GM in serum samples in 366

Figure 1. Geographical distribution of 66 cases of IA from FungiScope. Cases were reported from Germany (n = 30), France (n = 11), Argentina (n = 10), Turkey (n = 8), Spain (n = 4), Peru (n = 2), and Belgium (n = 1).

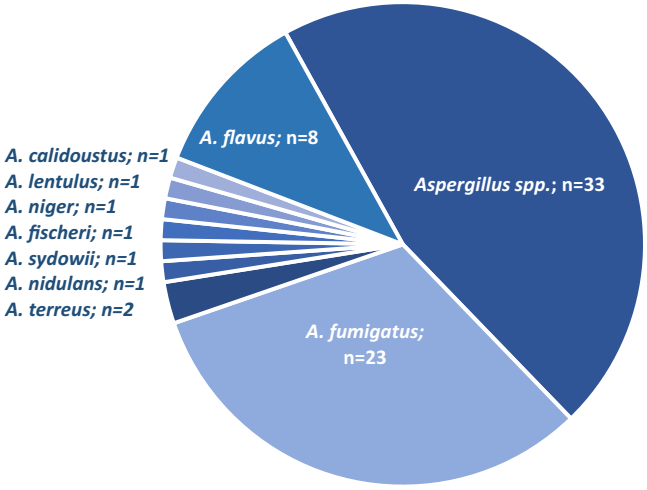

Figure 2. *Aspergillus* species distribution. Five patients had coinfections with more than one *Aspergillus* spp.

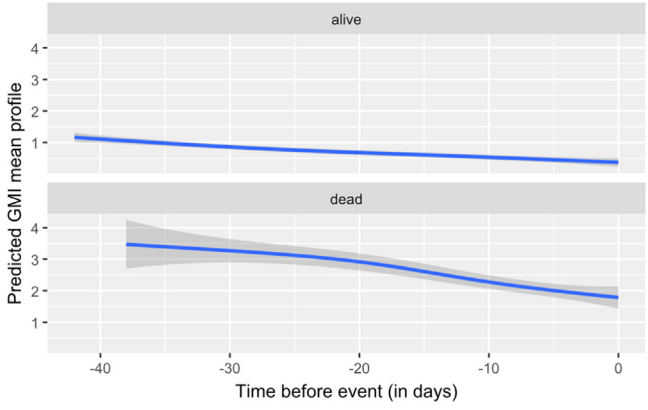

Figure 3. Predicted galactomannan index (GMI) mean profile from the joint model for the overall population. Time = day 0 marks each patient's event (dead or last follow-up alive); negative values represent days prior to that event. The two curves represent the model's average predicated GMI on each day prior to the event, separately for those who survived and those who eventually died.

measurements; in 47 measurements, the method of detection was not documented. For 29 measurements (7%), GMI were imputed to handle values recorded only as, e.g., < 0.5 or > 6. The joint model's day 7 GMI predictions correlated with the observed day 7 GMI at $r = 0.92$ (Supplementary Figure 1).

Decline in GMI was shown in patients who were alive at day 42 but also in patients who died before day 42, whereas the fatal cases started with and remained with a markedly higher GMI throughout (Figure 3). Patients who did not survive through day 42 showed a smaller decline or even increase in GMI within the first 7 days compared to the clear and constant decline of GMI in patients who were alive at day 42 (Supplementary Figures 2 and 3).

To assess discriminative performance of GMI change within the first 7 days for predicting survival at day 42, a ROC curve was generated, which yielded an area under the curve (AUC) of 0.656 (Supplementary Figure 4). In a Cox proportional hazards model, each > 0.25 GMI unit increase from baseline to day 7 was associated with a 15% higher risk of death, although the association was not statistically significant (HR 1.151, $P = 0.33$). When GMI was dichotomized at 1.0, patients with a baseline GMI ≥ 1 had more than twice the risk of dying by day 42 compared to those with a lower GMI, although again this association was not statistically significant (HR 2.107, $P = 0.19$).

A Kaplan–Meier curve comparing patients with baseline GMI ≥ 1 and those with GMI < 1 showed a trend toward higher mortality in the GMI ≥ 1 group during the later weeks of follow-up ($P = 0.36$) (Supplementary Figure 5).

GMI change from baseline vs clinical response

In the response analysis, predicted GMI on day 7 showed correlation with observed GMI ($r = 0.88$), indicating good model accuracy.

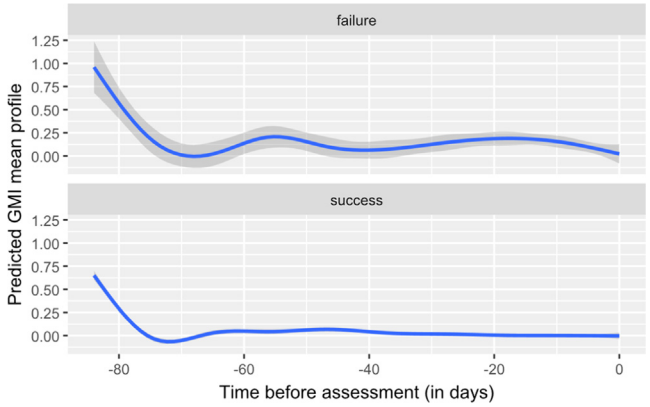

Figure 4. Predicted galactomannan index (GMI) mean profile in the 84 days between patients with failed (failure) and successful (success) treatment response. Time = day 0 represents the final assessment day (latest day 84). Negative values correspond to days before the final assessment day. Patients without an assessment at day 84 or an earlier final assessment were considered drop-outs and were excluded. Any negative values depicted on the *y*-axis result from the statistical smoothing of back-transformed GMI and are not indicative of actual negative measurements.

Over the 84-day follow-up, no clear difference in dynamics was observed between patients with successful vs failed treatment. However, patients who failed treatment appeared to have higher baseline GMI values (Figure 4).

The absolute change in serum GMI from baseline to day 7 was similar in patients with successful vs those with failed treatment by day 84, no separation was seen on the raw scale (Supplementary Figure 6), nor after log-transformation (Supplementary Figure 7).

A ROC curve for the change of GMI from baseline to day 7 yielded an AUC of 0.627, indicating modest discriminative ability (Supplementary Figure 8).

In a logistic regression model analyzing the association between day 7 GMI change and treatment success at day 84, the odds ratio per 0.25 GMI unit increase from baseline to day 7 was 1.004 ($P = 0.800$), suggesting no meaningful effect.

Until the time of diagnosis, 18 patients were receiving antifungal prophylaxis. The median baseline GMI was slightly lower in patients on prophylaxis compared with patients with no known prophylaxis (median GMI 1.10 vs 1.32, $P = 0.735$).

Explorative analyses

AFT received were available for 63 patients (95.5%). However, sample sizes in the first-week treatment subgroups were too small to show meaningful profiles (Supplementary Figure 9). In a Cox proportional hazard model, the azole group served as the reference category. Patients receiving polyenes had a higher hazard of death (HR 1.78, $P = 0.32$), although this association was not statistically significant. Comparison between monotherapy and combination therapy revealed that combination therapy was associated with a slightly lower hazard of death (HR 0.9035, $P = 0.894$), although again this did not reach statistical significance.

Documented azole resistance was identified in three patients. Two of these patients were treated with voriconazole, and one received liposomal amphotericin B in combination with voriconazole. All three patients died during follow-up; however, death was not attributed to invasive fungal infection in any case. The two patients treated with voriconazole alone died within 84 days after diagnosis.

Neutrophil count at the time of diagnosis was available for 31 patients, of whom 21 had severe neutropenia (< 100 neutrophils/μL) and 10 had counts $\geq 100/\mu$L. Patients with severe neutropenia were significantly more likely to present with baseline GMI ≥ 1 compared to those with counts of $\geq 100/\mu$L ($P = 0.027$). However, the median GMI values at baseline did not differ significantly between the two groups (1.1 vs 1.07, $P = 0.431$) (Table 2).

Discussion

Our analysis demonstrates that higher baseline GMI and a lack of early decline within the first-week were associated with increased mortality, and higher baseline GMI was linked to treatment failure, while no clear differences in GMI dynamics were observed between treatment responders and non-responders. Each $>$ 0.25 GMI unit increase by day 7 was associated with a 15% higher hazard of death. These findings suggest that early GMI changes may hold prognostic value for mortality, with similar, although not statistically significant, trends seen for AFT response.

GM testing is crucial in diagnosing IA, particularly in immunocompromised patients, and can be detected using Platelia *Aspergillus* enzyme immunoassay. The previous EORTC/MSG definitions [9] used the manufacturer's cutoff (ODI $\geq$ 0.5 in serum), whereas the 2020 consensus definitions adopted higher thresholds (ODI $\geq$ 1.0 in serum) to improve diagnostic specificity for the use in clinical trials [7]. The updated cutoffs aim to avoid overdiagnosis and trial bias in research settings but do not replace clinical judgment and are not intended for guiding routine therapy decisions [8]. Due to the real-life nature of our analysis, we chose to modify the updated cutoffs by including four possible cases of IA with positive GMI only (no other mycological evidence), of which three cases showed borderline positive GMI only ($\geq$ 0.5 and $<$ 0.7) but high likelihood of IA. One case was not classifiable according to the EORTC/MSG 2020 criteria due to missing documentation of a clinical feature, but again suggested a strong likelihood according to the treating physician.

Our findings align with previous preclinical data suggesting that GMI serves as a dynamic response marker [10]. In a rabbit model of invasive pulmonary aspergillosis (IPA), decreasing GMI correlated with AFT efficacy, fungal clearance, and improved survival [10]. This supports the rationale for using GMI trends in clinical settings to monitor treatment response in real time.

Monitoring treatment response usually involves invasive procedures (BAL) or radiation exposure (e.g., computed tomography scans), and it has been previously shown that serial BAL GM testing does not reliably correlate with clinical or radiologic response in patients with IPA [11]. While this may be due to technical variability in bronchoscopy, at the present time, serial BAL GM testing is currently not recommended for treatment monitoring [11], while serum measurements of a validated biomarker like GM are feasible to apply in routine care.

Several studies have demonstrated the clinical utility of serum GM as a prognostic biomarker in IA. It was previously shown that baseline serum GM and its early decay dynamics are powerful predictors of patient outcomes in IA [12]. For each unit increase in baseline GM, there was a 25% higher hazard of 6-week mortality, while a greater decline in GMI after 1 week correlated with improved survival, suggesting that baseline GM and early GM kinetics could serve as independent early surrogate biomarkers in antifungal therapy trials [12].

One study showed that a decline in GMI of more than 35% by the end of the first-week of treatment strongly predicts a favorable clinical response at 3 months, and trends in GMI clearance parallel radiologic and symptom improvement [4]. Another study identified an association between high baseline GMI and a poor day 45 outcome in patients with IA, whereas constantly negative GMI (< 0.5) during follow-up were associated with favorable outcomes [13]. It

Table 2
Comparison of clinical characteristics and galactomannan index (GMI) of two groups defined according to neutrophil counts at time of diagnosis.

	< 100 neutrophils/μL n = 21 (%)	≥ 100 neutrophils/μL n = 10 (%)	*P*-value
Biological sex			
Male	13 (61.9)	5 (50.0)	
Female	8 (38.1)	5 (50.0)	
Age groups			
1-6 years	5 (23.8)	2 (20.0)	
7-11 years	0 (0.0)	0 (0.0)	
12-16 years	1 (4.8)	1 (10.0)	
17-29 years	6 (28.6)	1 (10.0)	
30-49 years	1 (4.8)	2 (20.0)	
50-69 years	8 (38.1)	3 (30.0)	
70-89 years	0 (0.0)	1 (10.0)	
Underlying disease			
Haematological or oncological disease	20 (95.2)	8 (80.0)	
Allogenic HSCT	4 (19.0)	0 (0.0)	
Autologous HSCT	0 (0.0)	1 (10.0)	
SOT	1 (4.8)	1 (10.0)	
Acute GvHD	2 (9.5)	0 (0.0)	
IA according to EORTC/MSG criteria			
Proven	1 (4.8)	1 (10.0)	
Probable	17 (81.0)	7 (70.0)	
Possible	3 (14.3)	1 (10.0)	
Not classifiable	0 (0.0)	1 (10.0)	
Site of IA			
Pulmonary	18 (85.7)	9 (90.0)	
Disseminated (lung + paranasal sinuses)	3 (14.3)	0 (0.0)	
Disseminated (lung + brain)	0 (0.0)	1 (10.0)	
Survival of IA			
28 days[b]	18 (85.7)	9 (90.0)	$P = 1.0$
84 days[b]	15 (71.4)	4 (40.0)	$P = 0.127$
Baseline GMI, median [range][a]	1.1 [0.5-4.8]	1.07 [0.7-10.2]	$P = 0.431$
Baseline GMI < 1[a]	9 (42.9)	5 (50.0)	$P = 0.199$
Baseline GMI ≥ 1[a]	12 (57.1)	5 (50.0)	$P = 0.027$
Received steroids prior to IA diagnosis[b]			$P = 0.640$
Yes	15 (71.4)	7 (70.0)	
No	5 (23.8)	1 (10.0)	
Mold-active antifungal prophylaxis[c]			$P = 1.0$
Yes	8 (38.1)	4 (40.0)	
No	13 (61.9)	6 (60.0)	
Antifungal treatment for IA[d]			$P = 0.323$
Yes	21 (100.0)	9 (90.0)	
No	0 (0.0)	1 (10.0)	

GMI, galactomannan index; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis; SOT, solid organ transplantation.
[a] Kruskal–Wallis test.
[b] Fisher's exact test; for three patients unknown whether prophylaxis was administered (< 100 neutrophils/μL: $n = 1$; > 100 neutrophils/μL: $n = 2$).
[c] Fisher's exact test.
[d] Fisher's exact test.

was shown that on day 14, clinical evaluation was able to predict day 45 outcome [13].

A case report from 2023 observed that serum GM trends closely reflected radiologic improvement and neutrophil recovery during prolonged AFT in two immunocompromised adolescents with IPA [14]. These results underscore the potential of serum GM as a dynamic marker during prolonged antifungal therapy [14].

In our cohort, patients receiving antifungal prophylaxis showed a slightly lower median GMI compared with patients with no known prophylaxis (median GMI 1.10 vs 1.32, $P = 0.735$), which suggests that antifungal prophylaxis can suppress circulating GM, which may lead to an underestimation of IA if relying on GM alone.

A landmark study in patients from the isavuconazole licensing trial demonstrated that an increase in GMI of more than 0.25 units from baseline by day 7 was associated with an almost 10-fold higher risk of mortality, and each unit decrease of GMI by day 7 doubled the odds of a successful treatment outcome [15].

Our data are in concordance with those of Kovanda et al. [15], however, whereas their analysis focused on a cohort from a phase 3 clinical trial, our approach uses real-world data, thereby extending the applicability of GMI monitoring in diverse clinical settings. We modified and extended the methodology by introducing a dichotomous threshold at 1.0; patients with a baseline GMI ≥ 1 exhibited a twofold higher hazard of death by day 42 compared to those with GMI < 1. Moreover, we conducted additional exploratory analyses to further investigate the association between neutropenia and GMI levels. Patients with severe neutropenia (< 100 neutrophils/μL) were significantly more likely to present with GMI ≥ 1 at baseline compared with patients with ≥ 100 neutrophils/μL, indicating a higher fungal burden in patients with severe neutropenia [16]. In neutropenic patients, GMI might become positive earlier, making it a more sensitive diagnostic tool in this group [17].

If established as response and even outcome measure, serum GMI may also be used as a surrogate endpoint in clinical trials on invasive fungal diseases [18].

Limitations

Our study has limitations inherent to its retrospective registry-based design. The lack of a defined schedule for serum GM testing across patients may have introduced variability in assessing GM kinetics. To address this, imputation using a joint modelling

approach was necessary, introducing assumptions that may affect the robustness and generalizability of the findings. Some subgroup analyses, such as treatment types, neutropenia status at baseline, included small case numbers, limiting the reliability of comparative estimates and increasing the risk of type II error. Only patients with at least two GM measurements and documented outcomes were included in this analysis, potentially excluding those who deceased early or those with irregular follow-up. The specific assay used for determining GM was not documented in 47 measurements. As assay performance can influence GMI, the absence of this documentation may have introduced measurement heterogeneity that could not be accounted for in the analysis. Furthermore, azole resistance was not recorded in all patients with available isolates, potentially limiting outcome and GMI interpretation. These methodological constraints highlight the importance of prospective study designs with predefined sampling protocols to validate the prognostic utility of GMI trends.

Conclusion

Serum GMI serves as a non-invasive, predictive tool for estimating survival probability at onset of IA in a real-world analysis. Early GMI changes correlate with survival; thus, GMI increases should signal timely treatment adjustments and real-time therapeutic interventions to improve clinical outcomes.

Ethical approval and consent to participate

FungiScope was approved by the Ethics Committee of the Faculty of Medicine, University of Cologne, Germany (Identifier: 05-102) and all ethics committees of the participating trial sites.

Data availability

On reasonable and approved requests made to the corresponding author, data can be shared through secure online platforms.

Funding

The research leading to these results was conducted as part of the FungiScope registry study, which has received unrestricted grants in the past 5 years from Amplyx, Basilea Pharmaceutica, Cidara Therapeutics, F2G, Matinas BioPharma, Scynexis, and Pfizer Inc.

Author contributions

CT and DS: Data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing—original draft, writing—review and editing. OAC: Funding acquisition, investigation, methodology, project administration, resources, writing—review and editing. CSJ and ES: Investigation, validation, writing—review and editing. JAC, BH, DYK, DR, AHG, GAM, JDJ, NE, LLS, PK, AA, DD, RD, IFR, JMA, LM, and RKD: Investigation, writing—review and editing. JS: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing—original draft, writing—review and editing. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank all study team members for their effort and cooperation within this study. We thank Dr. Daniel Sabanés Bové (R-PACT) for statistical consulting.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108272.

References

[1] Wu Z, Wang L, Tan L, Wu J, Chen Z, Hu M. Diagnostic value of galactomannan in serum and bronchoalveolar lavage fluid for invasive pulmonary aspergillosis in non-neutropenic patients. *Diagn Microbiol Infect Dis* 2021;**99**(4):115274. doi:10.1016/j.diagmicrobio.2020.115274.

[2] Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018;**24**(Suppl 1):e1–38. doi:10.1016/j.cmi.2018.01.002.

[3] Hites M, Goicoechea Turcott EW, Taccone FS. The role of galactomannan testing to diagnose invasive pulmonary aspergillosis in critically ill patients. *Ann Transl Med* 2016;**4**(18):353. doi:10.21037/atm.2016.08.32.

[4] Chai LY, Kullberg BJ, Johnson EM, Teerenstra S, Khin LW, Vonk AG, et al. Early serum galactomannan trend as a predictor of outcome of invasive aspergillosis. *J Clin Microbiol* 2012;**50**(7):2330–6. doi:10.1128/jcm.06513-11.

[5] Nouér SA, Nucci M, Kumar NS, Grazziutti M, Barlogie B, Anaissie E. Earlier response assessment in invasive aspergillosis based on the kinetics of serum *Aspergillus* galactomannan: proposal for a new definition. *Clin Infect Dis* 2011;**53**(7):671–6. doi:10.1093/cid/cir441.

[6] Seidel D, Durán Graeff LA, Vehreschild M, Wisplinghoff H, Ziegler M, Vehreschild JJ, et al. FungiScope(™)-global emerging fungal infection registry. *Mycoses* 2017;**60**(8):508–16. doi:10.1111/myc.12631.

[7] Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020;**71**(6):1367–76. doi:10.1093/cid/ciz1008.

[8] Mercier T, Castagnola E, Marr KA, Wheat LJ, Verweij PE, Maertens JA. Defining galactomannan positivity in the updated EORTC/MSGERC consensus definitions of invasive fungal diseases. *Clin Infect Dis* 2021;**72**(Suppl_2):S89–94. doi:10.1093/cid/ciaa1786.

[9] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**(12):1813–21. doi:10.1086/588660.

[10] Gastine S, Hope W, Hempel G, Petraitiene R, Petraitis V, Mickiene D, et al. Pharmacodynamics of posaconazole in experimental invasive pulmonary aspergillosis: utility of serum galactomannan as a dynamic endpoint of antifungal efficacy. *Antimicrob Agents Chemother* 2021;**65**(2):e01574–20. doi:10.1128/aac.01574-20.

[11] Friedman DZP, Theel ES, Walker RC, Vikram HR, Razonable RR, Vergidis P. Serial bronchoalveolar lavage fluid *Aspergillus* galactomannan and treatment response in invasive pulmonary aspergillosis. *Open Forum Infect Dis* 2024;**11**(4):ofae114. doi:10.1093/ofid/ofae114.

[12] Koo S, Bryar JM, Baden LR, Marty FM. Prognostic features of galactomannan antigenemia in galactomannan-positive invasive aspergillosis. *J Clin Microbiol* 2010;**48**(4):1255–60. doi:10.1128/jcm.02281-09.

[13] Bergeron A, Porcher R, Menotti J, Poirot JL, Chagnon K, Vekhoff A, et al. Prospective evaluation of clinical and biological markers to predict the outcome of invasive pulmonary aspergillosis in hematological patients. *J Clin Microbiol* 2012;**50**(3):823–30. doi:10.1128/jcm.00750-11.

[14] Tragiannidis A, Linke C, Correa-Martinez CL, Herbrüggen H, Schaumburg F, Groll AH. Long-term kinetics of serum galactomannan during treatment of complicated invasive pulmonary aspergillosis. *J Fungi (Basel)* 2023;**9**(2):157. doi:10.3390/jof9020157.

[15] Kovanda LL, Kolamunnage-Dona R, Neely M, Maertens J, Lee M, Hope WW. Pharmacodynamics of isavuconazole for invasive mold disease: role of galactomannan for real-time monitoring of therapeutic response. *Clin Infect Dis* 2017;**64**(11):1557–63. doi:10.1093/cid/cix198.

[16] Cordonnier C, Botterel F, Ben Amor R, Pautas C, Maury S, Kuentz M, et al. Correlation between galactomannan antigen levels in serum and neutrophil counts in haematological patients with invasive aspergillosis. *Clin Microbiol Infect* 2009;**15**(1):81–6. doi:10.1111/j.1469-0691.2008.02122.x.

[17] Penack O, Rempf P, Graf B, Blau IW, Thiel E. *Aspergillus* galactomannan testing in patients with long-term neutropenia: implications for clinical management. *Ann Oncol* 2008;**19**(5):984–9. doi:10.1093/annonc/mdm571.

[18] Mercier T, Guldentops E, Lagrou K, Maertens J. Galactomannan, a surrogate marker for outcome in invasive aspergillosis: finally coming of age. *Front Microbiol* 2018;**9**:661. doi:10.3389/fmicb.2018.00661.