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OPEN PEER REVIEW

Nosocomial Fungal Infections in South of Iran: Epidemiology, Risk Factors, and Antifungal Susceptibility

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About this report

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1 Original submission

4 comments · 21 Apr 2026 – 21 Apr 2026

Referee 1 Reviewer

MAJOR REVISION 21 Apr 2026

Dear Authors,

Thank you for the opportunity to review this manuscript. The comments below present additional scientific observations by the reviewer that were not already part of the editorial-screening stage. The major comments focus on substantive methodological and reporting issues under the STROBE framework, while the minor comments address clarity, presentation, and editorial refinement.

This manuscript reports a retrospective cross-sectional hospital-based study conducted over 10 months in a tertiary referral center in Shiraz, Iran, aiming to estimate the rate of nosocomial fungal infections and describe associated risk factors, etiologic agents, infection sites, and antifungal susceptibility patterns. The topic is clinically relevant, particularly given the transplant-heavy case mix and the regional importance of invasive fungal infections. The combination of microbiology, molecular testing, and susceptibility data gives the study potential value for readers interested in hospital epidemiology and fungal disease management.

The manuscript's main strengths are the clinical relevance of the research question, the inclusion of a high-risk tertiary-care population, the attempt to distinguish colonization from proven/probable infection, and the presentation of local antifungal susceptibility findings that may be useful in a regional context. The study also addresses an underreported area in hospital epidemiology in the Middle East and therefore has potential practical value if the reporting and analytic framework are strengthened.

Major Comments:

1. Case-ascertainment pathway and denominator logic (STROBE):

> *The manuscript reports 12,941 admitted patients, then narrows this to 3,890 patients "who did not have any signs and symptoms of infection at the time of admission," and then to 153 patients suspected of having nosocomial fungal infection, of whom 40 were finally classified as having proven/probable infection; however, the operational pathway by which patients moved across these stages is not described with sufficient precision to allow readers to judge selection, surveillance intensity, and risk of under- or over-ascertainment (source: Methods; Results). The currently reported incidence of 1.03% is therefore difficult to interpret because it is calculated against the 3,890 enrolled patients rather than the full admitted population, while the text does not fully explain whether all eligible long-stay patients were systematically screened or only clinically triggered subsets were evaluated (source: Methods; Results).*
> *Author to-do list:*
>
> ** Clarify the exact surveillance pathway from all admissions to eligible patients, suspected cases, tested cases, and final proven/probable cases, including who was screened systematically and who was tested only after clinical suspicion arose (source: Methods; Results).*
> ** Define the primary denominator for the reported infection rate and justify why 40/3890, rather than another denominator, best represents the study objective (source: Abstract; Objectives; Results).*
> ** Add a concise patient-flow description in STROBE style, preferably with explicit inclusion counts at each stage and reasons for exclusion where applicable (source: Methods; Results; Figure 1; Figure 2).*
> ** Distinguish clearly between hospital-wide burden, cohort-specific incidence, and positivity among suspected cases so that readers do not conflate these different measures (source: Results).*

2. Definition of nosocomial fungal infection and classification consistency (STROBE):

The manuscript provides definitions for proven and probable invasive fungal infection, but the definition of "nosocomial" remains insufficiently operationalized for this specific study, especially because the inclusion criteria mention a hospital stay of ≥7 days, whereas the reported overall mean hospitalization among all admitted patients is 7.41 days with a range starting at 2.5 days, and the manuscript does not clearly state whether infection onset timing was verified for each confirmed case beyond general eligibility rules (source: Methods; Definition; Results). This matters because readers need confidence that reported infections were genuinely hospital-acquired rather than incubating or evolving from pre-admission colonization or community-acquired disease in highly immunocompromised patients (source: Background; Methods; Discussion).
Author to-do list:

** Define the study's nosocomial criterion explicitly in terms of timing of symptom onset, sampling date, or diagnostic confirmation relative to admission date (source: Methods; Definition).*
** State whether all 40 proven/probable cases met the same temporally verified hospital-acquired threshold and how this was checked from the records (source: Methods; Results).*
** Explain how pre-existing fungal colonization or pre-admission infection was excluded, especially in transplant, oncology, and ICU populations at high baseline risk (source: Methods; Results; Discussion).*
** Reconcile the ≥7-day inclusion rule with the broader hospitalization statistics reported for the whole hospital population so the eligibility framework is fully transparent (source: Methods; Table 1; Results).*

3. Risk-factor analysis remains descriptive and does not support causal or predictive interpretation (STROBE):

The manuscript identifies transplantation, hematologic disorders, and ICU stay as the most prevalent risk factors, and it states that ICU patients were significantly more affected than patients in other wards, yet the analytic strategy is limited to descriptive statistics and a briefly mentioned chi-square test without a clearly defined comparison framework, effect estimates, confidence intervals, or adjustment for confounding (source: Methods; Results). Because the study population appears highly heterogeneous across wards and underlying diseases, the current presentation does not allow readers to determine whether these are independent risk factors, correlated markers of illness severity, or simply the most common characteristics among infected patients (source: Table 2; Results; Discussion).
Author to-do list:

** Specify the exact comparison groups used for each claimed risk-factor analysis, including which denominator populations were compared with the infected cases (source: Methods; Results).*
** Report effect estimates with confidence intervals for the main risk-factor associations rather than relying only on frequency descriptions or isolated P values (source: Methods; Results).*
** Clarify whether multivariable analysis was considered and, if not performed, temper the language so that "risk factors" is not interpreted as evidence of independent association (source: Objectives; Methods; Discussion).*
** Distinguish clearly between descriptive characteristics of infected patients and analytically supported determinants of infection (source: Results; Discussion).*

4. Outcome definitions and infection-site reporting require tighter alignment with the diagnostic evidence (STROBE):

The manuscript reports liver, lung, brain, sinus, abdominal, and "other" infection sites, while also including PCR-positive aspergillosis cases and mixed diagnostic pathways based on culture, pathology, and molecular testing; however, the link between each anatomical site and the exact diagnostic evidence used for assigning that site is not sufficiently transparent (source: Definition; Table 2; Results). This affects interpretability because site-specific conclusions may differ substantially depending on whether cases were culture-confirmed, pathology-confirmed, or inferred from PCR plus clinical/radiological findings, particularly in the context of probable mold infections (source: Definition; Results; Discussion).

** Provide a clearer mapping between each infection site and the evidentiary basis used to classify it, separating pathology-proven, culture-proven, and PCR-supported cases where relevant (source: Definition; Results; Table 2).*
** Explain how "liver" and "brain" infection sites were assigned diagnostically and whether these represented invasive infection, abscess, dissemination, or another prespecified clinical category (source: Results; Table 2).*
** Clarify what is included under "Others*" and present that category more explicitly in the text or table footnote (source: Table 2).*
** Ensure that the wording of site-specific findings does not imply equal diagnostic certainty across proven and probable cases (source: Results; Discussion).*

5. Antifungal susceptibility results are extensive but insufficiently translated into clinically interpretable findings (STROBE):

The manuscript presents MIC distributions and geometric mean values for Candida and Aspergillus isolates, and it concludes that certain agents were the "most effective," but the interpretation framework is incomplete because clinical breakpoints or epidemiologic cutoff references are not integrated into the results tables or narrative interpretation (source: Sensitivity test; Results; Table 3). Without a clearer interpretive bridge, readers cannot determine whether lower MICs in this dataset truly indicate likely clinical utility across species, especially given the small numbers for several non-albicans Candida and mold isolates (source: Table 3; Discussion).
Author to-do list:

** State explicitly which CLSI breakpoint or epidemiologic cutoff framework was applied to each organism-drug pairing and where interpretation was not possible (source: Sensitivity test).*
** Separate descriptive MIC reporting from clinical claims of "effectiveness," especially for species-drug combinations with very small isolate counts (source: Results; Table 3).*
** Indicate which results should be interpreted cautiously because of low isolate numbers or absence of species-specific interpretive criteria (source: Table 3; Discussion).*
** Revise the discussion so that susceptibility conclusions remain proportional to the data actually generated in this single-center series (source: Results; Discussion).*

Minor Comments:

1. Tables and figures presentation:

The manuscript contains 3 tables and 3 figures, and each appears to be cited in the main text: Table 1, Table 2, Table 3, Figure 1, Figure 2, and Figure 3 are all explicitly referenced (source: Results). Presentation can still be improved by making the figure and table titles more self-contained, standardizing wording such as "study period" versus "study periods," and ensuring that every abbreviation used within tables/figures is defined directly in the legend or footnote rather than only in the main text (source: Table 1; Table 2; Table 3; Figure 1; Figure 2; Figure 3).

2. Language and style refinement:

Several sentences require English-language polishing for precision and readability. For example, "A Variety of fungal species..." should use lowercase "variety" and smoother phrasing; "were entered in the present study" is awkward and would read more clearly as "were included in the study"; "patients were suspicious for nosocomial fungal infections" should be revised to "patients were suspected of having nosocomial fungal infections"; and "The more frequent sites of fungal infection were the liver, lungs, and brain" would read better as "The most frequent sites..." (source: Abstract; Results). Additional examples include "The study was according to the ethical values...", which is grammatically unnatural and should be rewritten, and "Luliconazole and ISA were presented as most effective", which should be revised to "showed the lowest MIC values" or similarly precise wording (source: Ethical Approval; Results). A thorough native-level language edit would improve clarity and reduce ambiguity throughout the manuscript (source: Abstract; Methods; Results; Discussion).

3. Terminology consistency:

> *The manuscript alternates between "sensitivity," "susceptibility," "effective," and "ineffective" when discussing antifungal testing. For microbiology reporting, terminology should be standardized, with "antifungal susceptibility testing" used consistently and "effectiveness" reserved for clinical response only when outcome data support that claim (source: Sensitivity test; Results; Discussion).*

4. Statistical reporting style:

> *The manuscript would benefit from more standardized statistical reporting, including consistent spacing around P values, explicit reporting of test application, and clearer presentation of descriptive denominators in tables and text. For example, "P <0.05" should be formatted consistently, and frequencies in the narrative should routinely specify both numerator and denominator where the reference population could be misunderstood (source: Methods; Results; Table 2).*

5. Reference currency:

> *A small number of references are relatively old and should be reviewed for continued necessity or replacement with more recent sources where appropriate, particularly reference 12 (1999) and reference 13 (2001), unless these are being retained specifically because they describe foundational diagnostic methods used in the study (source: References). Where older methodological citations are kept, adding newer validation or implementation literature would strengthen the manuscript's contemporary relevance (source: References).*

Best regards,
Scientific Reviewer

Referee 2 Reviewer

MAJOR REVISION 21 Apr 2026

Dear Authors,

Thank you for submitting your manuscript to the journal. Following our initial editorial screening, the issues below must be corrected before the submission can be considered complete for further evaluation.

Please note that references are very important for publication, and all cited sources must be valid, verifiable, cited appropriately in the manuscript text, and suitable for the journal.

2-1- Case-ascertainment and denominator framework requires clarification:

What the author wrote: The manuscript reports that 12,941 patients were admitted, 3,890 patients entered the study, 153 patients were suspected of having nosocomial fungal infection, and 40 patients were classified as having proven/probable infection, but does not clarify the exact surveillance pathway or denominator logic used to support the reported infection rate of 1.03% (source: Methods; Results).
Why correction is required: This must be corrected because the manuscript is not fully evaluable without a clear patient-selection and case-ascertainment framework showing how the study cohort was derived and how the incidence denominator was defined (source: Methods; Results).
To do: Clarify the full screening pathway from all admissions to eligible patients, suspected cases, tested cases, and final confirmed cases, and define explicitly which denominator should be used for the main infection-rate estimate (source: Methods; Results; Figure 1; Figure 2).

2-2- Nosocomial definition and outcome classification require operational clarification:

What the author wrote: The manuscript states that inclusion required a hospital stay of ≥7 days and provides definitions for proven and probable fungal infection, but does not report a sufficiently explicit operational rule for confirming that each analyzed infection was hospital-acquired rather than pre-existing or evolving

from earlier colonization/infection risk (source: Methods; Definition; Results).
Why correction is required: This must be corrected because the manuscript is not fully verifiable without a clear and consistently applied temporal definition of nosocomial infection and a transparent link between infection-site assignment and the underlying diagnostic evidence (source: Methods; Definition; Table 2; Results).
To do: Define the exact timing rule used to classify infections as nosocomial, state how this was checked for all proven/probable cases, and reconcile site-specific classifications with the precise diagnostic evidence used for each site category (source: Methods; Definition; Table 2; Results).

2-3- Statistical and risk-factor reporting remains incomplete:

What the author wrote: The manuscript reports that transplantation, hematologic disorders, and ICU stay were the most prevalent risk factors and states that the number of ICU cases was significantly higher than that in other wards, but does not clarify the comparison groups, effect estimates, confidence intervals, or whether these findings are descriptive characteristics or analytically supported associations (source: Methods; Results; Table 2).
Why correction is required: This must be corrected because the manuscript is not fully evaluable without sufficient methodological detail regarding how risk-factor claims and ward-based comparisons were derived and interpreted (source: Methods; Results; Discussion).
To do: Provide the exact comparison framework for each reported association, report appropriate effect estimates with confidence intervals where feasible, and revise the wording so that unsupported causal or independent-risk interpretations are avoided when only descriptive analysis was performed (source: Methods; Results; Discussion).

2-4- Reference integrity requires correction:

What the author wrote: The manuscript contains 37 references, all of which appear to be cited in the manuscript text, but 10 references fail one or more validity checks due to recency and/or missing DOI/PMID verification, and the self-citation share is high (source: References; main text).
Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding reference validity, recency balance, and verifiability (source: References).
To do: Correct each invalid reference, validate all entries with DOI or PMID information where applicable, replace older references when justified alternatives exist, and review citation balance because self-citations exceed the preferred threshold (source: References).
Valid references: Ref 1 - Reddy et al., Ref 4 - Xiao et al., Ref 5 - Badiee et al., Ref 6 - Roman-Montes et al., Ref 7 - Badiee et al., Ref 8 - Suleyman et al., Ref 9 - Bassetti et al., Ref 10 - Panse et al., Ref 11 - Negm et al., Ref 19 - Donnelly et al., Ref 20 - Zingg et al., Ref 21 - Hosseini-Moghaddam et al., Ref 22 - Amona et al., Ref 23 - Cafardi et al., Ref 24 - Wang et al., Ref 25 - Mba et al., Ref 27 - Harrington et al., Ref 28 - Ture et al., Ref 29 - Patterson et al., Ref 30 - González-García et al., Ref 31 - Walther et al., Ref 32 - Mitchell et al., Ref 33 - Badiee et al., Ref 34 - Celestino de Souza et al., Ref 35 - Hivary et al., Ref 36 - Badiee et al., Ref 37 - Nabili et al. (source: References).
Invalid references:
Ref 2 - Walsh et al. — lacks DOI/PMID in the submitted citation entry and remains insufficiently verifiable in its current form (source: References).
Ref 3 - Badiee et al. — published in 2011 or earlier and is therefore invalid by recency unless a strong justification for retention is provided (source: References).
Ref 12 - Shin et al. — published in 1999 and is therefore invalid by recency unless a strong justification for retention is provided (source: References).
Ref 13 - Kami et al. — published in 2001 and is therefore invalid by recency unless a strong justification for retention is provided (source: References).
Ref 14 - CLSI — published in 2008 and lacks DOI/PMID, so it is invalid by recency and DOI/PMID-validity rules

(source: References).
Ref 15 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form (source: References).
Ref 16 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form (source: References).
Ref 17 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form (source: References).
Ref 18 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form (source: References).
Ref 26 - Obeed et al. — lacks DOI/PMID in the submitted citation entry and remains insufficiently verifiable in its current form (source: References).
What the author wrote: The manuscript contains six self-citations linked to manuscript authors, representing 16.2% of the full reference list (source: References; Authors' Contribution).
Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding balanced citation practice when self-citations exceed 10% of the reference list (source: References; Authors' Contribution).
To do: Review the self-citation balance, retain only those self-citations that are clearly necessary, and replace unnecessary self-citations with more directly relevant independent references where available (source: References).

Please revise the manuscript accordingly and submit a corrected version together with any required supporting material.

Kind regards,
Screening Reviewer

Associate Editor

MAJOR REVISION 21 Apr 2026

Dear Authors,

This original article examines the epidemiology, risk factors, infection sites, and antifungal susceptibility patterns of nosocomial fungal infections in a tertiary referral hospital in southern Iran. The manuscript addresses a clinically important topic with regional relevance and has the potential to make a useful contribution to the infectious diseases literature. At the same time, the current version requires substantial strengthening before it can be considered further.

The most valuable aspect of the manuscript is its focus on a high-risk hospital population in a setting where locally generated data on nosocomial fungal infections remain limited. The inclusion of microbiological, molecular, and susceptibility-related findings gives the study potential practical relevance for clinicians and hospital epidemiologists.

The scientific review indicates that the manuscript's main limitations lie in methodological transparency and reporting completeness rather than in topic selection. In particular, the current presentation does not yet provide sufficient clarity regarding case ascertainment, denominator choice, outcome classification, and the interpretation of risk factors and susceptibility findings. In addition, presentation and language issues reduce readability and make some of the findings appear less precise than they could be.

Title and abstract: 7/10
Introduction and rationale: 8/10
Methods rigor: 5/10

Results presentation: 6/10
Discussion and interpretation: 6/10
Reporting quality: 5/10
Language and structure: 6/10
Clinical relevance or scholarly value: 8/10
Overall quality: 6/10

In its present form, the manuscript appears promising but would require major revision before it could be reconsidered. A revised version should improve methodological clarity, strengthen the reporting framework, refine the presentation of results, and address the identified editorial and reference-related concerns in a thorough and consistent manner.

Kind Regards,
Associate Editor

Editor-in-Chief

MAJOR REVISION 21 Apr 2026

Dear Authors,

Thank you for submitting your manuscript entitled “Nosocomial Fungal Infections in South of Iran: Epidemiology, Risk Factors, and Antifungal Susceptibility.”

After editorial assessment and scientific review, we believe that the manuscript addresses a clinically relevant topic and has potential value, particularly because of its regional focus and its attention to hospital-acquired fungal infections in a high-risk patient population. However, the current version requires substantial revision before it can be considered further for publication. The main issues relate to methodological clarity, case-definition and denominator transparency, interpretation of the analytical findings, and the need to strengthen several reporting and reference-related aspects of the submission.

We therefore invite you to submit a thoroughly revised version of the manuscript that addresses the concerns raised during the review process. A revised submission will be reconsidered after careful evaluation of the extent and quality of the revisions.

Kind Regards,
Editor-in-Chief

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

----------> Reviewer (1) Comments <----------

Dear Editor

Thank you for your time in reviewing this manuscript. All change requests in the manuscript and for reviewer 1 are marked in red font and for reviewer 2 in blue font in the text. It should be noted that some of the content was expressed by two respected referees, which is shown in green.

Reviewer 1:

Thanks for your scientific comments. Revised parts were written in red font and some of the content was expressed by two respected referees, which is shown in green.

Major Comments:

1. Case-ascertainment pathway and denominator logic (STROBE):

The manuscript reports 12,941 admitted patients, then narrows this to 3,890 patients “who did not have any signs and symptoms of infection at the time of admission,” and then to 153 patients suspected of nosocomial fungal infection, of whom 40 were finally classified as proven/probable infection; however, the operational pathway by which patients moved across these stages is not described with sufficient precision to allow readers to judge selection, surveillance intensity, and risk of under- or over-ascertainment (source: Methods; Results). The currently reported incidence of 1.03% is therefore difficult to interpret because it is calculated against the 3,890 enrolled patients rather than the full admitted population, while the text does not fully explain whether all eligible long-stay patients were systematically screened or only clinically triggered subsets were evaluated (source: Methods; Results).

> Author to-do list:

> * Clarify the exact surveillance pathway from all admissions to eligible patients, suspected cases, tested cases, and final proven/probable cases, including who was screened systematically and who was tested only after clinical suspicion arose (source: Methods; Results).

Answer: In this study, surveillance was conducted in a stepwise manner: all admitted patients (n = 12,941) were considered as the source of population. From these, patients without signs of infection at admission and with hospital stay ≥7 days (n = 3,890) were included in this study for evaluating nosocomial fungal infections. Among these cases, patients who developed clinical, radiological, or laboratory suspicion of fungal infection (n = 153) underwent targeted mycological evaluation. Finally, 40 patients met criteria for proven or probable nosocomial fungal infection. Importantly, systematic screening was performed for all 3,890 patients. Diagnostic testing (such as culture, microscopy, PCR) for identifying the fungal infections were performed only in patients with clinical suspicion for these infections (n = 153). One hundred fifty-three patients were classified as proven, probable, and possible fungal infections. Figure 1 present the flowchart of patient' population.

It was revised in Abstract (lines 14-18), Method section. Lines 69-78, and Results section (lines 149-152).

> * Define the primary denominator for the reported infection rate and justify why 40/3890, rather than another denominator, best represents the study objective (source: Abstract; Objectives; Results).

Answer: Only 3890 patients had no symptoms of infection at the time of admission to the hospital. The other patients showed symptoms of infection (fever sometimes the only sign of an infection, chills, cough, sore throat or mouth, shortness of breath, nasal congestion, stiff neck, …) at the time of admission and were excluded from the study. Therefore, this number of 3890 was the best denominator for calculations in this study (Lines 69-87).

> * Add a concise patient-flow description in STROBE style, preferably with explicit inclusion counts at each stage and reasons for exclusion where applicable (source: Methods; Results; Figure 1; Figure 2).

Answer: It was added as figure1 (flowchart)

> * Distinguish clearly between hospital-wide burden, cohort-specific incidence, and positivity among suspected cases so that readers do not conflate these different measures (source: Results).

Answer: Hospital-wide burden, and positivity among suspected were presented in figure1 (flowchart).

- Definition of nosocomial fungal infection and classification consistency (STROBE):
> The manuscript provides definitions for proven and probable invasive fungal infection, but the definition of “nosocomial” remains insufficiently operationalized for this specific study, especially because the inclusion criteria mention hospital stay of ≥7 days, whereas the reported overall mean hospitalization among all admitted patients is 7.41 days with a range starting at 2.5 days, and the manuscript does not clearly state whether infection onset timing was verified for each confirmed case beyond general eligibility rules (source: Methods; Definition; Results). These matters because

readers need confidence that reported infections were genuinely hospital-acquired rather than incubating or evolving from pre-admission colonization or community-acquired disease in highly immunocompromised patients (source: Background; Methods; Discussion).

> Author to-do list:

> * Define the study's nosocomial criterion explicitly in terms of timing of symptom onset, sampling date, or diagnostic confirmation relative to admission date (source: Methods; Definition).

Answer: There is no universal definition of when a nosocomial fungal infection occurs because the incubation period of the disease is unknown. However, in general, nosocomial fungal infection usually begins after one week of hospitalization (R1, 2). In this study, nosocomial infection was defined as fungal infection occurring ≥7 days after hospital admission, based on the onset of clinical symptoms or radiological findings appeared, sampling was immediately performed and the necessary tests were done to determine the type of infection.
It was added in methods, definition lines 118-123.

1. Vazquez JA, Miceli MH, Alangaden G. Invasive fungal infections in transplant recipients. Ther Adv Infect Dis 2013;1(3):85–105.
2. Pappas PG, Kauffman CA, Andes DR. Clinical practice guideline for the management of candiadiasis; 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1–50.

> * State whether all 40 proven/probable cases met the same temporally verified hospital-acquired threshold and how this was checked from the records (source: Methods; Results).

Answer: This study was a cross sectional and is a complete original research that we were with the patients at all times in the hospital and diagnosis has been confirmed by reviewing the results of laboratory tests and evaluated the patient's clinical symptoms according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC-MSGERC) criteria.

It was added in definition lines 118-123 and result section Lines 180-181..

> * Explain how pre-existing fungal colonization or pre-admission infection was excluded, especially in transplant, oncology, and ICU populations at high baseline risk (source: Methods; Results; Discussion).

Answer: Colonization at the time of infection was examined in this study, and pre-existing fungal colonization without no symptoms of fungal infection during the study period was not examined. when patients presented signs on infection, colonization was evaluated by us. To minimize misclassification, pre-admission infection was excluded by evaluated the signs or symptoms of infection at admission time. Cases with evidence of pre-existing fungal infection or ongoing antifungal therapy at admission time were not included. Colonization detected early without clinical or radiological evidence was not classified as infection (line 68-77).

> * Reconcile the ≥7-day inclusion rule with the broader hospitalization statistics reported for the whole hospital population so the eligibility framework is fully transparent (source: Methods; Table 1; Results).

Answer: This threshold was used both as an inclusion criterion and as an operational definition of nosocomial acquisition. The overall hospital means stay (7.41 days) reflects all admissions, including short stays, whereas our study specifically targeted patients at risk of hospital acquired infections (lines 69-73 and 118-123).

Risk-factor analysis remains descriptive and does not support causal or predictive interpretation (STROBE):

> The manuscript identifies transplantation, hematologic disorders, and ICU stay as the most prevalent risk factors, and it states that ICU patients were significantly more affected than patients in other wards, yet the analytic strategy is limited to descriptive statistics and a briefly mentioned chi-square test without a clearly defined comparison framework, effect estimates, confidence intervals, or adjustment for confounding (source: Methods; Results). Because the study population appears highly heterogeneous across wards and underlying diseases, the current presentation does not allow readers to determine whether these are independent risk factors, correlated markers of illness severity, or simply the most common characteristics among infected patients (source: Table 2; Results; Discussion).

> Author to-do list:

> * Specify the exact comparison groups used for each claimed risk factor analysis, including which denominator populations were compared with the infected cases (source: Methods; Results).

> * Report effect estimates with confidence intervals for the main risk-factor associations rather than relying only on frequency descriptions or isolated P values (source: Methods; Results).

> * Clarify whether multivariable analysis was considered and, if not performed, temper the language so that “risk factors” is not interpreted as evidence of independent association (source: Objectives; Methods; Discussion).

> * Distinguish clearly between descriptive characteristics of infected patients and analytically supported determinants of infection (source: Results; Discussion).

Answer: This study is more descriptive and clinical, and I stated this point in the method and corrected the results data based on the descriptive study. The purpose of this study, as stated by the esteemed reviewer, was simply to report the most common organ involved in nosocomial invasive fungal infections. Determining a separate baseline for each group would harm the manuscript due to the limited samples and the nature of fungal infection, which is a rare disease. Therefore, in this study, we only report the frequency of the involved organ and nosocomial fungal infection in all patients admitted in the hospital during the study periods (Methods line 62).

Outcome definitions and infection-site reporting require tighter alignment with the diagnostic evidence (STROBE):

> The manuscript reports liver, lung, brain, sinus, abdominal, and “other” infection sites, while also including PCR-positive aspergillosis cases and mixed diagnostic pathways based on culture, pathology, and molecular testing; however, the link between each anatomical site and the exact diagnostic evidence used for assigning that site is not sufficiently transparent (source: Definition; Table 2; Results).

This affects interpretability because site-specific conclusions may differ substantially depending on whether cases were culture-confirmed, pathology-confirmed, or inferred from PCR plus clinical/radiological findings, particularly in the context of probable mold infections (source: Definition; Results; Discussion).

Author to-do list:

> * Provide a clearer mapping between each infection site and the evidentiary basis used to classify it, separating pathology-proven, culture-proven, and PCR-supported cases where relevant (source: Definition; Results; Table 2).

> * Explain how “liver” and “brain” infection sites were assigned diagnostically and whether these represented invasive infections, abscess, dissemination, or another prespecified clinical category (source: Results; Table 2).

> * Clarify what is included under “Others*” and present that category more explicitly in the text or table footnote (source: Table 2).

> * Ensure that the wording of site-specific findings does not imply equal diagnostic certainty across proven and probable cases (source: Results; Discussion).

Answer: Clinicians would send samples to the laboratory based on the patients' clinical and radiological symptoms, and then various tests would be performed to confirm the location of the infection. As written in the manuscript (lines 87-93) for site-specific findings in suspected patients, clinical samples, including midstream urine, wound swabs, sputum, bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF), pleural fluid, fluid in the abscess, and tissue biopsies

were examined microscopically (10% KOH smear) and cultured on SDA with chloramphenicol. Blood samples were cultured in BACTEC medium (Becton–Dickinson, Sparks, MD, USA). Data related to pathological findings, radiological and clinical symptoms were extracted from the patient's file, and based on all the data, the type of disease and the site of infection were determined. In clinical practice, when a patient shows symptoms of the disease but we cannot determine the specific site of the disease, it is called fever of unknown origin (FUO). In this study, the site of infection in patients suffering from FUO was designated as "other". these patients had two positive PCR results along with clinical symptoms. (Definition lines 138-140).

In this study, the site of infection in patients suffering from FUO was designated as "other". these patients had two positive PCR results along with clinical symptoms.

Antifungal susceptibility results are extensive but insufficiently translated into clinically interpretable findings (STROBE):

> The manuscript presents MIC distributions and geometric mean values for Candida and Aspergillus isolates, and it concludes that certain agents were the “most effective,” but the interpretation framework is incomplete because clinical breakpoints or epidemiologic cutoff references are not integrated into the results tables or narrative interpretation (source: Sensitivity test; Results; Table 3). Without a clearer interpretive bridge, readers cannot determine whether lower MICs in this dataset truly indicate likely clinical utility across species, especially given the small numbers for several non-albicans *Candida* and mold isolates (source: Table 3; Discussion).

> Author to-do list:

> * State explicitly which CLSI breakpoint or epidemiologic cutoff framework was applied to each organism-drug pairing and where interpretation was not possible (source: Sensitivity test).

Answer: It is important to identify the etiologic agent and species isolated from nosocomial diseases. The number of patients with nosocomial fungal diseases is small, but due to the high mortality rate, the disease has clinical value. In this study, we performed susceptibility determination on isolated strains, but determining the epidemiological cut-off is possible when the number of each isolate isolated is at least 100. The number of species isolated from patients in this study was less than 100. Therefore, in this study, we reported the MIC value, and the lower MIC value present the high sensitivity of the isolated fungus. It can be used in the clinic. Foe the best presentation of the CLSI breakpoint, Table 4 was added.

> * Separate descriptive MIC reporting from clinical claims of “effectiveness,” especially for species-drug combinations with very small isolate counts (source: Results; Table 3)

Answer: It was corrected in the text.

> * Indicate which results should be interpreted cautiously because of low isolate numbers or absence of species-specific interpretive criteria (source: Table 3; Discussion).

Answer: The sentence was added (Lines 306-309).

> * Revise the discussion so that susceptibility conclusions remain proportional to the data actually generated in this single-center series (source: Results; Discussion).

Answer: The sentence was added (Lines 312-318).

Minor Comments:

1. Tables and figures presentation:

> The manuscript contains 3 tables and 3 figures, and each appears to be cited in the main text: Table 1, Table 2, Table 3, Figure 1, Figure 2, and Figure 3 are all explicitly referenced (source: Results). Presentation can still be improved by making the figure and table titles more self-contained, standardizing wording such as “study period” versus “study periods,” and ensuring that every abbreviation used within tables/figures is defined directly in the legend or footnote rather than only in the main text (source: Table 1; Table 2; Table 3; Figure 1; Figure 2; Figure 3).

Answer: It was revised.

2. Language and style refinement:

> Several sentences require English-language polishing for precision and readability. For example, “A Variety of fungal species...” should use lower-case “variety” and smoother phrasing; “were entered in the present study” is awkward and would read more clearly as “were included in the study”; “patients were suspicious for nosocomial fungal infections” should be revised to “patients were suspected of having nosocomial fungal infections”; and “The more frequent sites of fungal infection were the liver, lungs, and brain” would read better as “The most frequent sites...” (source: Abstract; Results). Additional examples include “The study was according to the ethical values...” which is grammatically unnatural and should be rewritten, and “Luliconazole and ISA were presented as most effective” which should be revised to “showed the lowest MIC values” or similarly precise wording (source: Ethical Approval; Results). A thorough native-level language edit would improve clarity and reduce ambiguity throughout the manuscript (source: Abstract; Methods; Results; Discussion).

Answer: The sentences were corrected.

3. Terminology consistency:

> The manuscript alternates between “sensitivity,” “susceptibility,” “effective,” and “ineffective” when discussing antifungal testing. For microbiology reporting, terminology should be standardized, with “antifungal susceptibility testing” used consistently and “effectiveness” reserved for clinical response only when outcome data support that claim (source: Sensitivity test; Results; Discussion).

Answer: The manuscript was revised based on recommendations.

4. Statistical reporting style:

> The manuscript would benefit from more standardized statistical reporting, including consistent spacing around P values, explicit reporting of test application, and clearer presentation of descriptive denominators in tables and text. For example, “P <0.05” should be formatted consistently, and frequencies in the narrative should routinely specify both numerator and denominator where the reference population could be misunderstood (source: Methods; Results; Table 2).

Answer: Fungal infections are more common in people with compromised immune systems, and the number of these infections in clinical practice is lower than viral and microbial infections. For this reason, the study population was heterogeneous in this study, and due to the small number of

patients in each group, valid statistical calculations cannot be provided. Therefore, we present the study in a descriptive manner.

5. Reference currency:

> A small number of references are relatively old and should be reviewed for continued necessity or replacement with more recent sources where appropriate, particularly reference 12 (1999) and reference 13 (2001), unless these are being retained specifically because they describe foundational diagnostic methods used in the study (source: References). Where older methodological citations are kept, adding newer validation or implementation literature would strengthen the manuscript's contemporary relevance (source: References).

Answer: The manuscript was revised based on recommendations. However, we agree that, in general, updating older references with more recent literature can improve the manuscript. However, references 12 (1999) and 13 (2001) have been retained intentionally, as they describe the original and foundational diagnostic methodologies that were directly employed in our molecular testing procedures.

----------> END of Reviewer (1) Comments <----------

----------> **Reviewer (2) Comments** <----------

Thanks for your scientific comments. Revised parts were written in blue font, and some of the content was provided by two respected referees, as shown in green.

Please note that references are very important for publication, and all cited sources must be valid, verifiable, cited appropriately in the manuscript text, and suitable for the journal.

2-1- Case-ascertainment and denominator framework requires clarification:

What the author wrote: The manuscript reports that 12,941 patients were admitted, 3,890 patients entered the study, 153 patients were suspected of nosocomial fungal infection, and 40 patients were classified as proven/probable infection, but does not clarify the exact surveillance pathway or denominator logic used to support the reported infection rate of 1.03% (source: Methods; Results). **Why correction is required:** This must be corrected because the manuscript is not fully evaluable without a clear patient-selection and case-ascertainment framework showing how the study cohort was derived and how the incidence denominator was defined (source: Methods; Results). **To do:** Clarify the full screening pathway from all admissions to eligible patients, suspected cases, tested cases, and final confirmed cases, and define explicitly which denominator should be used for the main infection-rate estimate (source: Methods; Results; Figure 1; Figure 2).

Answer: these comments were revised in the Abstract (lines 14-18), Methods (lines 69-78); Results (149-152); and one figure (Figure 1) inserted to the manuscript.

2-2- Nosocomial definition and outcome classification require operational clarification: What the author wrote: The manuscript states that inclusion required hospital stay of ≥7 days and provides definitions for proven and probable fungal infection, but does not report a sufficiently explicit operational rule for confirming that each analyzed infection was hospital-acquired rather than pre-existing or evolving from earlier colonization/infection risk (source: Methods; Definition; Results).

Why correction is required: This must be corrected because the manuscript is not fully verifiable without a clear and consistently applied temporal definition of nosocomial infection and a transparent link between infection-site assignment and the underlying diagnostic evidence (source: Methods; Definition; Table 2; Results).

To do: Define the exact timing rule used to classify infections as nosocomial, state how this was checked for all proven/probable cases, and reconcile site-specific classifications with the precise diagnostic evidence used for each site category (source: Methods; Definition; Table 2; Results).

Answer: There is no comprehensive definition of what causes nosocomial fungal infection because the incubation period of the disease is unknown. However, in general, nosocomial fungal infection usually begins after one week of hospitalization (R1, 2). In this study, nosocomial infection was defined as fungal infection occurring ≥7 days after hospital admission, based on the onset of clinical symptoms or radiological findings appeared, sampling was immediately performed and the necessary tests were done to determine the type of infection.

It was added in definition lines 118-123.

17. Vazquez JA, Miceli MH, Alangaden G. Invasive fungal infections in transplant recipients. Ther Adv Infect Dis 2013;1(3):85–105.

18. Pappas PG, Kauffman CA, Andes DR. Clinical practice guideline for the management of candiadiasis; 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1–50.

Answer: Clinicians would send samples to the laboratory based on the patients' clinical and radiological symptoms, and then various tests would be performed to confirm the location of the infection. As written in the manuscript (lines 86-92) for site-specific findings in suspected patients, clinical samples, including midstream urine, wound swabs, sputum, bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF), pleural fluid, fluid in the abscess, and tissue biopsies, were examined microscopically (10% KOH smear) and cultured on SDA with chloramphenicol. Blood samples were cultured in BACTEC medium (Becton–Dickinson, Sparks, MD, USA). Data related to pathological findings, radiological and clinical symptoms were extracted from the patient's file, and based on all the data, the type of disease and the site of infection were determined. In clinical practice, when a patient shows symptoms of the disease but we cannot determine the specific site of the disease, it is called fever of unknown origin (FUO). In this study, the site of infection in patients suffering from FUO was designated as "other". These patients had two positive PCR results along with clinical symptoms (Definition lines 138-141).

2-3- Statistical and risk-factor reporting remains incomplete:

What the author wrote: The manuscript reports that transplantation, hematologic disorders, and ICU stay were the most prevalent risk factors and states that ICU cases were significantly higher than in other wards, but does not clarify the comparison groups, effect estimates, confidence intervals, or whether these findings are descriptive characteristics or analytically supported associations (source: Methods; Results; Table 2).

Why correction is required: This must be corrected because the manuscript is not fully evaluable without sufficient methodological detail regarding how risk-factor claims and ward-based comparisons were derived and interpreted (source: Methods; Results; Discussion).

To do: Provide the exact comparison framework for each reported association, report appropriate effect estimates with confidence intervals where feasible, and revise the wording so that unsupported causal or independent-risk interpretation is avoided when only descriptive analysis was performed (source: Methods; Results; Discussion).

Answer: Fungal infections are more common in people with compromised immune systems, and the number of these infections in clinical practice is lower than viral and microbial infections. For this reason, the study population was heterogeneous in this study, and due to the small number of patients in each group, valid statistical calculations cannot be provided. Therefore, we revised the study in a descriptive manner.

2-4- Reference integrity requires correction:

What the author wrote: The manuscript contains 37 references, all of which appear cited in the manuscript text, but 10 references fail one or more validity checks due to recency and/or missing DOI/PMID verification, and the self-citation share is high (source: References; main text).

Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding reference validity, recency balance, and verifiability (source: References).

To do: Correct each invalid reference, validate all entries with DOI or PMID information where applicable, replace older references when justified alternatives exist, and review citation balance because self-citations exceed the preferred threshold (source: References).

Valid references: Ref 1 - Reddy et al., Ref 4 - Xiao et al., Ref 5 - Badiee et al., Ref 6 - Roman-ontes et al., Ref 7 - Badiee et al., Ref 8 - Suleyman et al., Ref 9 - Bassetti et al., Ref 10 - Panse et al., Ref 11 - Negm et al., Ref 19 - Donnelly et al., Ref 20 - Zingg et al., Ref 21 - Hosseini-Moghaddam et al., Ref 22 - Amona et al., Ref 23 - Cafardi et al., Ref 24 - Wang et al., Ref 25 - Mba et al., Ref 27 - Harrington et al., Ref 28 - Ture et al., Ref 29 - Patterson et al., Ref 30 - González-García et al., Ref 31 - Walther et al., Ref 32 - Mitchell et al., Ref 33 - Badiee et al., Ref 34 - Celestino de Souza et al., Ref 35 - Hivary et al., Ref 36 - Badiee et al., Ref 37 - Nabili et al. (source: References).

Invalid references:

Ref 2 - Walsh et al. — lacks DOI/PMID in the submitted citation entry and remains insufficiently verifiable in its current form. (source: References)

Answer: It was corrected.

Ref 3 - Badiee et al. — published in 2011 or earlier and is therefore invalid by recency unless a strong justification for retention is provided. (source: References)

Answer: It was omitted.

Ref 12 - Shin et al. — published in 1999 and is therefore invalid by recency unless a strong justification for retention is provided. (source: References)

Answer: We agree that, in general, updating older references with more recent literature can improve the manuscript. However, reference 12 (1999) have been retained intentionally, as they describe the original and foundational diagnostic methodologies that were directly employed in our molecular testing procedures.

Ref 13 - Kami et al. — published in 2001 and is therefore invalid by recency unless a strong justification for retention is provided. (source: References)

Answer: We agree that, in general, updating older references with more recent literature can improve the manuscript. However, reference 13 (2001) have been retained intentionally, as they describe the original and foundational diagnostic methodologies that were directly employed in our molecular testing procedures.

Ref 14 - CLSI — published in 2008 and lacks DOI/PMID, so it is invalid by recency and DOI/PMID-validity rules. (source: References)

Answer: We would like to clarify that CLSI (Clinical and Laboratory Standards Institute) documents are not journal articles but official guidelines/standards. As such, they typically do not have DOI or PMID identifiers.

Ref 15 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal’s reference-validity rules in its current form. (source: References)

Answer: We would like to clarify that CLSI (Clinical and Laboratory Standards Institute) documents are not journal articles but official guidelines/standards. As such, they typically do not have DOI or PMID identifiers.

Ref 16 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form. (source: References)

Answer: We would like to clarify that CLSI (Clinical and Laboratory Standards Institute) documents are not journal articles but official guidelines/standards. As such, they typically do not have DOI or PMID identifiers.

Ref 17 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form. (source: References)

Answer: We would like to clarify that CLSI (Clinical and Laboratory Standards Institute) documents are not journal articles but official guidelines/standards. As such, they typically do not have DOI or PMID identifiers.

Ref 18 - CLSI — lacks DOI/PMID in the submitted citation entry and is therefore invalid under the journal's reference-validity rules in its current form. (source: References)

Answer: We would like to clarify that CLSI (Clinical and Laboratory Standards Institute) documents are not journal articles but official guidelines/standards. As such, they typically do not have DOI or PMID identifiers.

Ref 26 - Obeed et al. — lacks DOI/PMID in the submitted citation entry and remains insufficiently verifiable in its current form. (source: References)

Answer: It doesn’t have any DOI.

What the author wrote: The manuscript contains six self-citations linked to manuscript authors, representing 16.2% of the full reference list (source: References; Authors' Contribution).

Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding balanced citation practice when self-citations exceed 10% of the reference list (source: References; Authors' Contribution).

To do: Review the self-citation balance, retain only those self-citations that are clearly necessary, and replace unnecessary self-citations with more directly relevant independent references where available (source: References).

Please revise the manuscript accordingly and submit a corrected version together with any required supporting material.

Answer: The self-citations decreased.

Screening Reviewer

----------> END of Reviewer (2) Comments <----------

2 Revision 1

4 comments · 31 May 2026 – 15 Jun 2026

Referee 3 Reviewer

ACCEPT 31 May 2026

Dear Author
With regard
I have carefully read your article.
I would like to inform you that, considering the importance of the topic of fungal infections and the lack of studies on antifungal susceptibility testing in Iran, your article is approved for publication in this journal.
Wishing you success

Referee 4 Reviewer

MINOR REVISION 1 Jun 2026

Dear authors,
I appreciate the time and effort you spent preparing a manuscript on nosocomial fungal infection in southern Iran. In my opinion, your topic is relatively novel, clinically relevant, and falls well within the scope of the journal. I believe that your manuscript can be accepted after some revisions. Please address my comments:
1-Please provide further explanation of the study methodology in the method section of the abstract.
2-Did you consult an epidemiologist when conceptualizing your study?
3-As you mentioned in the study limitations, the lack of clinical data, e.g., previous antibiotic medication, chemotherapy treatment, etc., restricts the interpretation of the data. Please further highlight this issue in the discussion section. You can use published studies from Iran in this regard.
Regards,

Associate Editor

MINOR REVISION 15 Jun 2026

Minor revision

Editor-in-Chief

MINOR REVISION 15 Jun 2026

Minor revision

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor-in-Chief,

We would like to sincerely thank you and the reviewers for the careful evaluation of our manuscript. We appreciate the constructive comments and suggestions, which have significantly helped us improve the quality of our work.

We have carefully addressed all comments raised by the reviewers. A point-by-point response to each comment is provided below, and all corresponding revisions have been highlighted in yellow.

We hope the revised manuscript meets the journal's standards and remain grateful for the opportunity to resubmit our work.

Thank you for your time and consideration.

Sincerely,
Hadis Jafarian
Assistant professor of medical mycology,
Professor Alborzi Clinical Microbiology Research Center,
Shiraz University of Medical Sciences,

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Reviewers' Comments:

----------> Reviewer (1) Comments <----------
Dear Author
With regard
I have carefully read your article
I would like to inform you that considering the importance of the topic of fungal infections and the lack of studies on antifungal susceptibility testing in Iran, your article is approved for publication in this journal
Wishing you success

Answer: We sincerely thank the reviewer for the positive evaluation of our manuscript and for recognizing the importance of this topic. We greatly appreciate the reviewer's encouraging comments and support for the publication of our work.

----------> END of Reviewer (1) Comments <----------

----------> Reviewer (2) Comments <----------
Dear authors,
I appreciate your time and effort spent on preparing a manuscript on nosocomial fungal infection in the south of Iran. In my opinion, your topic is relatively novel, clinically relevant, and falls well within the scope of the journal. I believe that your manuscript can be accepted after some

revisions. Please address my comments:
1-Please provide further explanations regarding study methodology in the method section of the abstract.

Answer: Thank you for this comment. Due to the journal's abstract word-limit requirements, the methodological description in the original abstract was intentionally kept brief. However, we agree that additional methodological details would improve clarity. Therefore, the Methods section of the abstract has been revised. (lines 11-17, page 1)

2-Did you consult an epidemiologist for conceptualizing your study?

Answer: No formal consultation with an epidemiologist was undertaken during the conceptualization of this study. However, the study design was developed by a multidisciplinary team with expertise in medical mycology, infectious diseases, and clinical microbiology. Furthermore, established international definitions and guidelines, including the EORTC-MSGERC criteria, were followed to ensure methodological validity.

3-As you mentioned in the study limitations, lack of clinical data e.g., previous antibiotic medication, chemotherapy treatment, etc restricts data interpretations. Please further highlight this issue in the discussion section. You can use published studies in Iran in this regard.

Answer: Thank you for this comment. We agree that the lack of detailed clinical information may have limited the interpretation of our findings. Accordingly, we have expanded the section to further emphasize this limitation and to compare our findings with previous studies from Iran (references 39 and 40). We have also clarified that the absence of these data prevented a more comprehensive assessment of risk factors in our study population. (lines 317-322, page 18)

----------> END of Reviewer (2) Comments <----------

3 Revision 2

1 comment · 17 Jul 2026

Editor-in-Chief

ACCEPT 17 Jul 2026

Accept