



# Fast and Fusariosis: a systematic review and case report of a rapidly fatal central nervous system infection

Jason D. Vadhan<sup>1</sup>, Alyssa J. Melo<sup>2</sup>, Jeffery C. Shogan<sup>3</sup>, Vishal Singh<sup>4</sup>, Maria Carrillo<sup>4</sup>

<sup>1</sup>Department of Emergency Medicine, UT Southwestern Medical Center, Dallas, TX, USA; <sup>2</sup>Department of Internal Medicine, Georgetown University Medical Center, Washington, DC, USA; <sup>3</sup>Nova Southeastern University, College of Osteopathic Medicine, Ft. Lauderdale, FL, USA; <sup>4</sup>Department of Critical Care, Advent Health Orlando, Orlando, FL, USA

*Correspondence to:* Jason D. Vadhan, DO. Department of Emergency Medicine, UT Southwestern Medical Center, 5200 Harry Hines Blvd., Dallas, TX 75235, USA. Email: Jason.vadhan@phhs.org.

**Background:** Immunocompromised transplant recipients are at risk for fungal infections. *Fusarium spp.*, however, are a ubiquitous environmental fungus that has rarely been reported to cause invasive central nervous system (CNS) infection in patients post solid organ transplant.

**Case Description:** We report a 57-year-old male with a recent heart transplant on immunosuppressive therapy who presented to the emergency department with right eye pain, headache, and focal neurologic deficits, and was subsequently diagnosed with CNS Fusariosis and endophthalmitis. Following intensive care and operative management, the patient ultimately suffered from acute transplant rejection and passed away shortly thereafter. One day following the surgery, the patient demonstrated signs of acute heart failure, and underwent emergent right heart catheterization with endomyocardial biopsy that revealed acute transplant rejection. Unfortunately, given the advanced stage of his infection coupled with transplant rejection, palliative care was consulted, and the patient was discharged to hospice.

**Conclusions:** This is the 21st reported case of CNS Fusariosis. Of the reported cases, skin lesions were the most common presenting symptom (52.4%). Altered mental status was the most common neurologic symptom (23.8%). The cerebral cortex was the most frequently involved brain region involved (33.3%). Despite aggressive treatment, the mortality rate is extremely high (9.5%). We recommend a high index of suspicion and aggressive treatment for CNS Fusariosis given its heterogenous presentation, increasing number of reported cases, and fulminant disease course.

**Keywords:** Fusariosis; immunocompromised; central nervous system (CNS); CNS infection; case report

Received: 25 December 2020; Accepted: 24 June 2022; Published: 30 July 2022.

doi: 10.21037/jecm-21-125

View this article at: <https://dx.doi.org/10.21037/jecm-21-125>

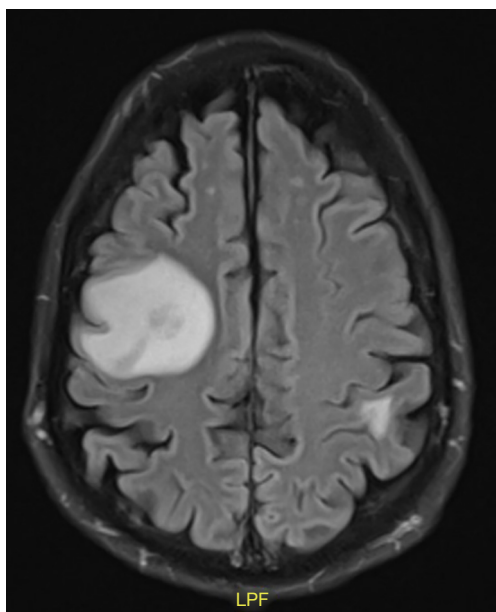
## Introduction

*Fusarium* is a ubiquitous fungal species commonly found in soil, water, and plants that can cause infections in immunocompetent as well as immunocompromised people. Immunocompetent patients are more likely to suffer from local skin infections, whereas immunosuppressed people are susceptible to invasive infections (1). Most *Fusarium* infections are caused by *F. solani*, *F. oxysporum*, and *F. moniliforme* (1). When infections do arise, it is most often spread via skin or respiratory tracts, which can arise as

localized necrotic tissue lesions in the lungs or skin (1).

Although invasive Fusariosis is exceedingly uncommon, the prognosis is poor, with mortality approaching as high as 90%, and with many cases being from patients with hematologic malignancies or following stem cell transplants (1-4). Infections following organ transplant are even more uncommon, with no previous case following a heart transplant.

Given the rarity of this condition and the necessity for rapid diagnosis and appropriate management, we present a case of central nervous system (CNS) Fusariosis, as well as a



**Figure 1** Large enhancing intraparenchymal lesion, measuring up to 15 mm × 13 mm in the right frontoparietal lesion with mild restricted diffusion with significant surrounding FLAIR hyperintensity suggesting vasogenic edema. FLAIR, fluid attenuated inversion recovery.

thorough review of previously documented cases of systemic Fusariosis, as well as a discussion of available diagnostic modalities and available interventions to guide the critical care physician in managing patients with this rare condition. We present the following article in accordance with the CARE reporting checklist (available at <https://jccm.amegroups.com/article/view/10.21037/jccm-21-125/rc>).

### Case presentation

A 57-year-old immunocompromised male with a previous medical history of orthotopic heart transplant secondary to ischemic cardiomyopathy one-month prior presented to the emergency department with a three-day history of unremitting generalized headache, right eye pain, and unilateral eye redness. He denied any systemic symptoms, including fever, chills, vision changes, dizziness, dysarthria, focal weakness, paresthesia, nausea, or vomiting. Physical exam was remarkable for left facial droop and 4/5 muscle strength in the left upper and lower extremity.

Laboratory studies revealed hyponatremia at 128 mEq/L and a leukocytosis of  $16.3 \times 10^3$  cells/microL but were otherwise unremarkable. He reported being adherent

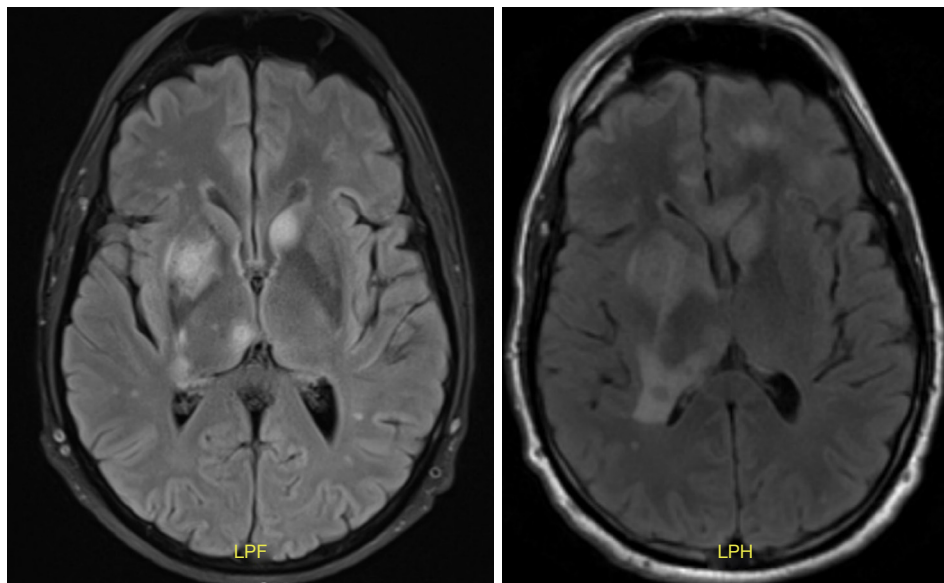
to his immunosuppressive regimen, which consisted of tacrolimus, mycophenolate, and prednisone, as well as his infection prophylaxis regimen which included nystatin, valganciclovir, and trimethoprim/sulfamethoxazole. Given the focal neurologic signs, a computed tomography (CT) head and MRI brain was ordered, and demonstrated over 10 enhancing intraparenchymal lesions, the largest being in the frontoparietal region and measuring 15 mm × 13 mm (Figure 1).

The patient was admitted for probable infectious *vs.* metastatic etiology, and neurosurgery, ophthalmology, and infectious disease were consulted. The patient's eye pain was diagnosed as iritis and improved with prednisone drops. On the second day of admission, the patient developed worsening nausea and bilateral upper extremity tremors. The patient began seizing and subsequently required endotracheal intubation for airway protection. An emergent repeat CT head was performed and revealed no acute changes or intracranial bleed. Lumbar puncture revealed a clear, colorless fluid with normal opening pressure, neutrophilic pleocytosis, elevated protein (63 mg/dL) with a normal glucose level. Cerebrospinal fluid VDRL, Cryptococcus antigen, HSV-1 PCR, and HSV-2 PCR, Toxoplasma IgG, and gram stain and culture were all negative. Blood, sputum, and urine cultures were negative. A microbial cell-free DNA test (Karius<sup>®</sup> Redwood City, CA) was positive for *Fusarium solani*.

The patient was immediately started on intravenous amphotericin B and voriconazole, and his immunosuppressive agents were temporarily reduced. On hospital day eight, the patient's headache and right eye pain suddenly worsened. Physical exam demonstrated right pupillary dilation prompting repeat imaging, which illustrated increased abscesses size and worsening surrounding edema. The patient underwent emergent neurosurgical drainage and biopsy, which was consistent with Fusariosis spp. The patient was also administered intravitreal antifungal therapy for the *Fusarium* endophthalmitis. Post-surgical repeat MRI demonstrated multiple new lesions and worsening edema (Figure 2).

One day following the surgery, the patient demonstrated signs of acute heart failure, and underwent emergent right heart catheterization with endomyocardial biopsy that revealed acute transplant rejection. Unfortunately, given the advanced stage of his infection coupled with transplant rejection, palliative care was consulted, and the patient was discharged to hospice.

All procedures performed in this study were in accordance



**Figure 2** Subsequent brain MRI with and without IV contrast following surgical resection of the right parietal lesion demonstrates worsening periventricular lesions with worsening midline shift. Left image is hospital day 1, right image is hospital day 8. IV, intravenous; MRI, magnetic resonance imaging.

with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

The PubMed database and all major infectious disease and critical care journals were searched during December 2021 using the keywords “Fusariosis”, “CNS”, “Invasive”, and “Disseminated”, alone or in combination to obtain articles fitting the inclusion and exclusion criteria. The inclusion criteria were CNS Fusariosis involving any region of the brain. Cases of Fusariosis not invading the brain structures, as well as non-Fusariosis fungal infections invading the CNS, were excluded.

To date, only 21 cases of CNS Fusariosis have been reported since 1974 (Table 1) (1,3,5-21). The outcomes of these cases remained poor, with only two cases noting survival following discovery and treatment of the infection. The age of discovery spanned from one to 76 years old, with no age bracket demonstrating a higher propensity for infection. However, the mean age of discovery is 37.63 years (95% CI: 25.6 to 45.6 years). The most common region

of brain involvement was the cerebral cortex (Figure 3), however it can arise anywhere within the brain structures, and demonstrates little preference for any particular region. In addition, the most common neurologic disturbance was related to altered mental status; however, the most common presenting symptoms overall was related to skin and respiratory involvement, as previous studies have suggested (Table 2) (1,3,5-21).

The clinical presentation of infection with *Fusarium* is vast, ranging from localized infection of the skin, nails, or eyes in immunocompetent individuals, to invasive and disseminated forms in the immunocompromised. Sites of invasive infection most often include the skin, eyes, lungs, and sinuses; less commonly involved are the bones, joints, and such as this case, the brain (2,4,22). Skin manifestations typically present as multiple painful erythematous nodules with centralized necrosis (via angioinvasion), resembling a target-like appearance (4). Given the prevalence of skin-derived Fusariosis among systemic disease, a thorough dermatologic examination is highly recommended, carefully assessing for the presence of skin or nail infections. Following skin involvement, the respiratory system is the second most common gateway for systemic infection (22). One final unique characteristic of invasive Fusariosis compared to other CNS fungal infections is its higher incidence of ophthalmologic related symptoms, including endophthalmitis

**Table 1** Summary of reported cases of CNS Fusariosis

Author, year	Patient age (years)	Predisposing condition	CNS location	Extra-CNS location	Presenting symptom
Abramowsky, 1974	2	Burn	Cerebral cortex	Skin, kidney, heart	Skin lesion
Agamanolis, 1991	15	Leukemia	Meninges	Skin	AMS, skin lesions
Anaissie, 1986	53	Multiple myeloma	Not specified	Skin, blood, heart, lung, GI, kidneys	Pneumonia, skin lesions
Anten, 2008	53	Unspecified cancer	Cerebral cortex	Lungs, skin	Fever, AMS
Antunes, 1998	Not specified	Not specified	Meninges	Not specified	Not specified
Bleggi-Torres, 1996	6	Aplastic anemia	Brainstem, cerebellum	Skin, lung	Skin lesion
Chen, 2017	65	None	Brain stem, cerebellum	None	AMS
Garcia, 2015	50	Leukemia	Cerebral cortex	Not specified	AMS
Kleinschmidt-Demasters, 2009	76	Leukemia	Cerebellum	Skin	Skin lesion
Lortholary, 2010	Not specified	Not specified	Not specified	Not specified	Not specified
Mehta, 2014	20	Leukemia	Thalamus, cerebellum, cerebral cortex	Skin, blood	Fever, skin lesions
Muhammed, 2013	23	Kidney transplant	Meninges	Blood	Nausea, vomiting, headache
Njambi, 2007	53	Leukemia	Cerebral cortex	Not specified	Not specified
Nucci, 2003	55	Lung transplant	Not specified	Skin, lung, intestines, kidney	Skin lesion
Schwartz, 2015	1	Aplastic anemia	Not specified	Skin, lung, blood	Skin lesions
Schwartz, 2015	15	Leukemia	Cerebral cortex	Lung	Respiratory distress, hemoptysis
Steinberg, 1983	17	Infectious mononucleosis	Brain stem	Skin	Gastrointestinal distress, skin lesion
Stropnicki, 2021	65	Liver transplant	Cerebral cortex, cerebellum, brain stem	None	Pupillary difference
Turra, 2020	13	Leukemia	Not specified	Skin, blood	Skin lesions, facial paralysis, AMS
Vadhan, 2020 (present case)	57	Heart transplant	Cerebral cortex	Eye	Headache, eye pain
Vincent, 2003	76	Leukemia	Cerebellum	Skin	Skin lesion

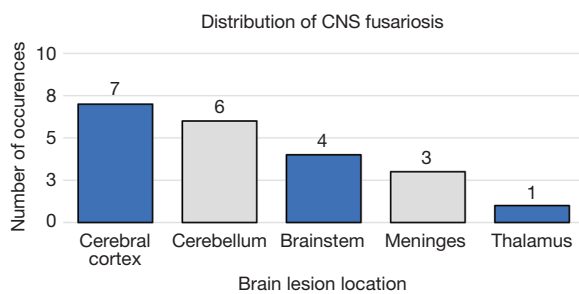
CNS, central nervous system; AMS, altered mental status; GI, gastrointestinal.

or chorioretinitis, as was the case in our patient (23).

The gold standard diagnosis of Fusariosis is tissue culture. Blood cultures in patients with invasive Fusariosis are limited, with only 60% sensitivity (11,24). Paradoxically, an *Aspergillus* galactomannan antigen assay can detect *Fusarium* infections, however given the clinical similarities between *Aspergillus* and *Fusarium spp.*, this may be a source

of confusion, despite having similar treatment strategies (24). More recently, the utilization of cell-free DNA (cfDNA) plasma extraction with next-generation sequencing has enabled rapid, accurate, and noninvasive testing for invasive fungal infections (25). For this patient, cfDNA was used to confirm the diagnosis.

Treating invasive Fusariosis remains a clinical challenge



**Figure 3** Distribution of CNS Fusariosis. The most common location for CNS Fusariosis is the cerebral cortex (33.33%). CNS, central nervous system.

**Table 2** Most common presenting symptoms

Presenting symptom	Incidence
Skin lesion	11
AMS	5
Respiratory distress	2
GI distress	2
Fever	2
Facial paralysis	1
Headache	1
Eye pain	1
Pupillary changes	1

AMS, altered mental status; GI, gastrointestinal.

due to the high drug resistance rate, which contributes to its high mortality rate (4). Nonetheless, invasive management involves a two-tailed approach: first, voriconazole and amphotericin B, or Posaconazole should be administered (4,26,27). Second, the patient's innate immunocompromised status (specifically neutropenia) must be reversed, as the most important risk factor for contracting invasive Fusariosis and the overall prognosis is the neutropenic status (4,11,23,28). Unfortunately, data to support the use of granulocyte colony-stimulating factor and granulocyte transfusions in these patients is limited (28).

In patients at risk of herniation, emergent surgical resection is recommended and can alleviate compression and control infection spread; however, its impact on clinical outcomes is inconclusive (4). Unfortunately, regardless of therapeutic interventions, the outcome is nearly always fatal if neutrophil recovery is not achieved (1). A summary of recommendations for the diagnostic workup and available

treatment strategies for invasive Fusariosis can be seen in Nucci *et al.*, 2007 (2). It is important to note that our patient was not neutropenic, further emphasizing the severity of this aggressive infection.

## Conclusions

Patients with invasive Fusariosis most commonly have a history of immunocompromised status and typically present with dermatologic, respiratory, or as in this case, ophthalmologic symptoms. Unfortunately, despite aggressive treatment with potent systemic antifungal therapies and neurosurgical resection, clinical outcomes remain poor. Given this, physicians must maintain a high index of suspicion for CNS Fusariosis among immunocompromised individuals because delay in diagnosis and treatment will almost assuredly result in catastrophic consequences. In addition, given the paucity of reported cases and lack of positive outcomes, we urge further research regarding CNS Fusariosis with the goal of improving treatment outcomes of this devastating disease.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <https://jccm.amegroups.com/article/view/10.21037/jccm-21-125/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://jccm.amegroups.com/article/view/10.21037/jccm-21-125/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Stropnický P, Heß K, Becker T, et al. Disseminated cerebral fusariosis in a liver-transplant patient: A case report and review of the literature. *Z Gastroenterol* 2021. [Epub ahead of print]. doi: 10.1055/a-1535-2981.
2. Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev* 2007;20:695-704.
3. Agamanolis DP, Kalwinsky DK, Krill CE Jr, et al. Fusarium meningoencephalitis in a child with acute leukemia. *Neuropediatrics* 1991;22:110-2.
4. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. *Clin Microbiol Infect* 2014;20 Suppl 3:27-46.
5. Abramowsky CR, Quinn D, Bradford WD, et al. Systemic infection by fusarium in a burned child. The emergence of a saprophytic strain. *J Pediatr* 1974;84:561-4.
6. Anaissie E, Kantarjian H, Jones P, et al. Fusarium. A newly recognized fungal pathogen in immunosuppressed patients. *Cancer* 1986;57:2141-5.
7. Anten S, Heddema ER, Visser O, et al. Images in haematology. Cerebral fungal abscess in a patient with acute promyelocytic leukaemia. *Br J Haematol* 2008;140:253.
8. Antunes NL, Hariharan S, DeAngelis LM. Brain abscesses in children with cancer. *Med Pediatr Oncol* 1998;31:19-21.
9. Bleggi-Torres LF, de Medeiros BC, Neto JZ, et al. Disseminated *Fusarium* sp. infection affecting the brain of a child after bone marrow transplantation. *Bone Marrow Transplant* 1996;18:1013-5.
10. Chen YJ, Chou CL, Lai KJ, et al. Fusarium Brain Abscess in a Patient with Diabetes Mellitus and Liver Cirrhosis. *Acta Neurol Taiwan* 2017;26(3):128-32.
11. Garcia RR, Min Z, Narasimhan S, et al. Fusarium brain abscess: case report and literature review. *Mycoses* 2015;58:22-6.
12. Kleinschmidt-Demasters BK. Disseminated Fusarium infection with brain abscesses in a lung transplant recipient. *Clin Neuropathol* 2009;28:417-21.
13. Lortholary O, Obenga G, Biswas P, et al. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010;54:4446-50.
14. Mehta A, Bellam N. Disseminated fusariosis during acute myelogenous leukemia induction treatment. *Blood* 2014;123:3379.
15. Muhammed M, Anagnostou T, Desalermos A, et al. Fusarium infection: report of 26 cases and review of 97 cases from the literature. *Medicine (Baltimore)* 2013;92:305-16.
16. Njambi S, Huttova M, Kovac M, et al. Fungal neuroinfections: rare disease but unacceptably high mortality. *Neuro Endocrinol Lett* 2007;28 Suppl 2:25-6.
17. Nucci M. Emerging moulds: *Fusarium*, *Scedosporium* and *Zygomycetes* in transplant recipients. *Curr Opin Infect Dis* 2003;16:607-12.
18. Schwartz KL, Sheffield H, Richardson SE, et al. Invasive Fusariosis: A Single Pediatric Center 15-Year Experience. *J Pediatric Infect Dis Soc* 2015;4:163-70.
19. Steinberg GK, Britt RH, Enzmann DR, et al. Fusarium brain abscess. Case report. *J Neurosurg* 1983;58:598-601.
20. Turra N, Acosta A, Incoronato A, et al. Multisystemic fusariosis with fulminant evolution. *An Bras Dermatol* 2020;95:645-8.
21. Vincent AL, Cabrero JE, Greene JN, et al. Successful voriconazole therapy of disseminated *Fusarium solani* in the brain of a neutropenic cancer patient. *Cancer Control* 2003;10:414-9.
22. Batista BG, Chaves MA, Reginatto P, et al. Human fusariosis: An emerging infection that is difficult to treat. *Rev Soc Bras Med Trop* 2020;53:e20200013.
23. McCarthy M, Rosengart A, Schuetz AN, et al. Mold infections of the central nervous system. *N Engl J Med* 2014;371:150-60.
24. Tortorano AM, Esposto MC, Prigitano A, et al. Cross-reactivity of *Fusarium* spp. in the Aspergillus Galactomannan enzyme-linked immunosorbent assay. *J Clin Microbiol* 2012;50:1051-3.
25. Hong DK, Blauwkamp TA, Kertesz M, et al. Liquid biopsy for infectious diseases: sequencing of cell-free plasma to detect pathogen DNA in patients with invasive fungal disease. *Diagn Microbiol Infect Dis* 2018;92:210-3.
26. Al-Hatmi AMS, Bonifaz A, Ranque S, et al. Current

- antifungal treatment of fusariosis. *Int J Antimicrob Agents* 2018;51:326-32.
27. Ortoneda M, Capilla J, Pastor FJ, et al. Efficacy of liposomal amphotericin B in treatment of systemic murine fusariosis. *Antimicrob Agents Chemother*

- 2002;46:2273-5.
28. Kadri SS, Remy KE, Strich JR, et al. Role of granulocyte transfusions in invasive fusariosis: systematic review and single-center experience. *Transfusion* 2015;55:2076-85.

doi: 10.21037/jeccm-21-125

**Cite this article as:** Vadhan JD, Melo AJ, Shogan JC, Singh V, Carrillo M. Fast and Fusariosis: a systematic review and case report of a rapidly fatal central nervous system infection. *J Emerg Crit Care Med* 2022;6:24.