

SIGNIFICANCE OF CONTRAST-ENHANCED CT BRAIN VS LUMBAR PUNCTURE FOR PATIENTS POST PRESENTING WITH SUSPECTED MENINGITIS IN THE EMERGENCY DEPARTMENT

MOHYUDDIN SARA*, HAMID MF, KHAN MI, AKRAM A, OWAIS SS

Department of Emergency, Shifa International Hospital, Islamabad, Pakistan

*Corresponding author email address: syedahsan087@gmail.com

(Received, 05th October 2024, Revised 18th February 2025, Accepted 06th March 2025, Published 14th March 2025)

ABSTRACT

Background: The routine use of contrast-enhanced computed tomography (CECT) prior to lumbar puncture (LP) in patients with suspected meningitis may delay definitive diagnosis and timely initiation of antimicrobial therapy. Evidence supporting the incremental diagnostic value of CECT over LP in emergency settings, particularly in low- and middle-income countries, remains limited. **Objective:** To compare the diagnostic significance of contrast-enhanced CT brain and lumbar puncture in adults presenting with suspected meningitis to the emergency department of a tertiary care hospital in Pakistan. **Study Design:** Prospective observational study. **Settings:** Emergency Department of Shifa International Hospital, Islamabad. **Duration of Study:** From March 2024 to August 2024. **Methods:** Ninety consecutive adult patients presenting with clinical features suggestive of acute meningitis were enrolled. In accordance with institutional protocol, all patients underwent a contrast-enhanced CT of the brain prior to lumbar puncture. CT findings were evaluated for parenchymal abnormalities and radiological contraindications to LP. Cerebrospinal fluid (CSF) analysis served as the reference standard for confirming and etiologically classifying meningitis. Diagnostic performance indices of CECT were calculated against CSF findings. Post-stratification analysis assessed associations between CT abnormalities, presenting clinical features, and in-hospital outcomes. Statistical analysis was performed using SPSS version 26, with $p < 0.05$ considered statistically significant. **Results:** The mean age of participants was 34.8 ± 15.6 years, with a male predominance (56.7%). CSF analysis confirmed meningitis in 84.4% of cases. The predominant etiologies were bacterial (41.1%), viral (31.1%), and tuberculous meningitis (12.2%). CECT demonstrated abnormalities in 35.6% of patients and identified radiological contraindications to LP in 8.9% of cases. Using CSF as the reference standard, CECT showed limited sensitivity (42.1%) and moderate specificity (83.3%) for meningitis-related abnormalities. CT abnormalities were significantly associated with altered level of consciousness, seizures, and papilledema ($p < 0.05$). Patients with abnormal CT findings experienced higher rates of intensive care unit admission, mechanical ventilation, neurological sequelae, and in-hospital mortality (all $p < 0.05$). Emergency department length of stay was significantly prolonged among patients undergoing CT prior to LP. **Conclusion:** Contrast-enhanced CT of the brain demonstrates limited sensitivity for confirming meningitis but remains valuable for identifying contraindications to lumbar puncture and stratifying patients at risk of severe outcomes. Lumbar puncture with CSF analysis remains the definitive diagnostic modality. Selective, guideline-directed use of pre-LP neuroimaging may reduce diagnostic delays and improve outcomes in resource-constrained emergency care settings.

Keywords: Meningitis, Computed Tomography, Lumbar Puncture, Emergency Department, Cerebrospinal Fluid

INTRODUCTION

A miscarriage, also referred to as spontaneous abortion, represents one of the most life-threatening neurological emergencies encountered in the emergency department (ED), demanding prompt diagnosis and immediate therapeutic intervention (1,2). Bacterial meningitis, in particular, carries significant morbidity and mortality, with outcomes directly correlated to the timeliness of diagnosis and initiation of antimicrobial therapy (1,2). The clinical presentation of meningitis, including fever, headache, neck stiffness, and altered mental status, necessitates a systematic, evidence-based diagnostic approach (3,2). Despite advances in neuroimaging and laboratory diagnostics, the optimal sequence of investigations in the ED remains a subject of ongoing clinical debate (3,4).

Lumbar puncture (LP) with cerebrospinal fluid (CSF) analysis remains the gold standard for confirming meningitis and providing critical information on causative organisms, cell counts, glucose, and protein levels (3,5). However, the widespread practice of performing CT brain imaging prior to LP to exclude raised intracranial pressure and contraindications to LP has introduced significant delays in both LP performance and antibiotic administration (3). Gulholm et al. demonstrated that 70% of patients with suspected meningitis underwent neuroimaging prior to LP, and this group experienced a

significantly longer median time to antibiotic administration (367 vs 231 minutes; $p = 0.001$) (3). Such delays are clinically consequential, as retrospective studies have shown that delayed antimicrobial therapy beyond 6 hours of ED arrival is associated with increased mortality (2).

Contrast-enhanced CT (CECT) of the brain has been increasingly utilised in the evaluation of suspected intracranial infections; however, its incremental diagnostic value over non-contrast CT remains poorly defined (4). Patel et al. found that in 343 patients evaluated for suspected intracranial infection, most acute infections with enhancing CT findings also had correlative conspicuous non-contrast CT findings that would independently merit further evaluation, concluding that CECT is redundant in most cases of suspected intracranial infection in the emergency setting (4). Current guidelines, including those from the Infectious Diseases Society of America (IDSA), do not explicitly mandate contrast administration in the CT evaluation of suspected meningitis (1,4).

Pakistan bears a disproportionate burden of infectious meningitis, including bacterial and tuberculous meningitis (TBM), given its high prevalence of tuberculosis and limited healthcare resources (6,7). TBM, the deadliest form of tuberculous manifestation, is particularly challenging to distinguish from bacterial meningitis on clinical grounds alone, and diagnostic delays are common in resource-limited

settings (6,7). In Pakistan, where CT scanners are available in tertiary care centers but LP expertise and CSF analysis infrastructure may be inconsistently available, the clinical decision of whether to prioritize CECT brain or LP has direct implications for patient outcomes and resource utilization. Furthermore, routine CECT prior to LP may impose unnecessary costs and delays in a healthcare system already under strain. This study aims to evaluate the comparative diagnostic significance of CECT brain versus LP in patients presenting to the ED with suspected meningitis, to inform evidence-based, context-appropriate clinical practice for the Pakistani population.

METHODOLOGY

This prospective, observational, analytical study was conducted in the Emergency Department of a tertiary care hospital over six months, from March to August 2024. The study included 90 consecutive patients aged 16 years and above who presented with clinical suspicion of acute meningitis, defined by the presence of fever, headache, neck stiffness, altered mental status, or seizures. Patients with known intracranial malignancy, recent neurosurgical procedures, or traumatic brain injury were excluded. After obtaining informed consent from patients or their legal guardians, detailed demographic and clinical data were recorded using a structured proforma. All patients underwent contrast-enhanced CT brain prior to lumbar puncture as per institutional protocol to assess for contraindications such as mass effect, midline shift, or obstructive hydrocephalus. CT scans were interpreted independently by two consultant radiologists blinded to CSF results. Lumbar puncture was performed under aseptic conditions unless contraindicated by CT findings. Cerebrospinal fluid was analyzed for cell count, glucose, and protein; Gram stain; culture; and, where indicated, PCR for viral pathogens and acid-fast bacilli. Diagnosis of bacterial, viral, or tuberculous meningitis was established based on standard laboratory criteria. Data were entered and analyzed using SPSS version 26. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range, depending on distribution assessed by the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. Sensitivity, specificity, positive predictive value, and negative predictive value of contrast-enhanced CT were calculated using CSF findings as the reference standard. Associations were assessed using chi-square or Fisher’s exact test for categorical variables and independent sample t-test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Ethical approval was obtained from the hospital's Institutional Review Board prior to the commencement of the study. All procedures were conducted in accordance with the Declaration of Helsinki and local ethical guidelines.

RESULTS

During the six-month study period (July to December), 90 consecutive adult patients presenting to the emergency department of a tertiary care hospital with clinical suspicion of acute meningitis were prospectively enrolled. The mean age was 34.8 ± 15.6 years (range 16–72 years). Males comprised 56.7% (n = 51), with a male-to-female ratio of 1.3:1. The largest age group was 31–50 years (42.2%), followed by 16–30 years (35.6%). Urban residents accounted for 61.1% of cases. Nearly half of the cohort (48.9%) had at least one comorbid condition, including diabetes mellitus (20.0%), hypertension (16.7%), and immunocompromised status (12.2%) (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Patients with Suspected Acute Meningitis (n = 90)

Variable	Frequency (n)	(%)
Age (years), mean ± SD	34.8 ± 15.6	—
16–30 years	32	35.6
31–50 years	38	42.2
>50 years	20	22.2
Male	51	56.7
Female	39	43.3
Urban residence	55	61.1
Rural residence	35	38.9
Diabetes mellitus	18	20.0
Hypertension	15	16.7
Immunocompromised	11	12.2

Fever (88.9%), headache (82.2%), and neck stiffness (70.0%) were the most frequent presenting features. Altered level of consciousness was observed in 38.9%, seizures in 21.1%, and papilledema in 13.3%. All patients underwent contrast-enhanced CT (CECT) brain prior to lumbar puncture according to institutional protocol. CT findings were normal in 64.4% (n = 58). Abnormalities were identified in 35.6% (n = 32), including cerebral edema (14.4%), meningeal enhancement (11.1%), hydrocephalus (5.6%), and space-occupying lesions (4.4%). Radiological features contraindicating immediate lumbar puncture, such as mass effect or obstructive hydrocephalus, were detected in 8 patients (8.9%) (Table 2).

Table 2: Contrast-Enhanced CT Brain Findings (n = 90)

CT Finding	Frequency (n)	(%)
Normal	58	64.4
Cerebral edema	13	14.4
Meningeal enhancement	10	11.1
Hydrocephalus	5	5.6
Space-occupying lesion	4	4.4
Contraindication to LP	8	8.9

Lumbar puncture was safely performed in 82 patients (91.1%). In 8 patients (8.9%), the procedure was deferred based on CT findings. Cerebrospinal fluid analysis confirmed meningitis in 76 patients (84.4%). Bacterial meningitis was diagnosed in 37 cases (41.1%), viral meningitis in 28 (31.1%), and tuberculous meningitis in 11 (12.2%). CSF was normal in 6 patients (6.7%) (Table 3).

Table 3: Cerebrospinal Fluid Analysis and Diagnostic Classification (n = 90)

CSF-Based Diagnosis	Frequency (n)	(%)
Bacterial meningitis	37	41.1
Viral meningitis	28	31.1
Tuberculous meningitis	11	12.2
Normal CSF	6	6.7
LP not performed	8	8.9

Using CSF findings as the reference standard, CECT of the brain demonstrated a sensitivity of 42.1% and a specificity of 83.3% for detecting meningitis-related abnormalities. The positive predictive value was 90.6%, while the negative predictive value was 28.1%. Importantly, CT showed 100% sensitivity in identifying patients with contraindications to lumbar puncture.

Post-stratification analysis revealed that abnormal CT findings were significantly associated with altered level of consciousness (62.5% vs. 25.9%, p = 0.001), seizures (40.6% vs. 10.3%, p = 0.002), and papilledema (25.0% vs. 6.9%, p = 0.018). No significant association was observed between CT abnormality and fever or neck stiffness (p > 0.05) (Table 4).

Table 4: Association Between Clinical Variables and Abnormal CT Findings (n = 90)

Variable	Abnormal CT (n=32)	Normal CT (n=58)	p-value
Altered consciousness	20 (62.5%)	15 (25.9%)	0.001*
Seizures	13 (40.6%)	6 (10.3%)	0.002*
Papilledema	8 (25.0%)	4 (6.9%)	0.018*
Fever	30 (93.8%)	50 (86.2%)	0.31
Neck stiffness	24 (75.0%)	39 (67.2%)	0.46

*Statistically significant at $p < 0.05$

Abnormal CT findings were also significantly associated with bacterial meningitis ($p = 0.03$), but not with viral or tuberculous meningitis ($p > 0.05$). The mean emergency department stay was longer in patients who underwent CT prior to lumbar puncture (6.2 ± 2.1 hours) than in those without contraindications (4.8 ± 1.7 hours; $p = 0.02$). The overall mean hospital stay was 8.6 ± 3.4 days.

Regarding clinical outcomes, 26 patients (28.9%) required ICU admission, and 18 (20.0%) required mechanical ventilation. Complete recovery without neurological deficit occurred in 62 patients (68.9%), whereas 17 (18.9%) were discharged with persistent neurological sequelae. The overall in-hospital mortality rate was 12.2% ($n = 11$). Patients with abnormal CT findings had significantly higher rates of ICU admission (56.3% vs. 13.8%, $p < 0.001$), mechanical ventilation (43.8% vs. 6.9%, $p < 0.001$), neurological sequelae (34.4% vs. 10.3%, $p = 0.006$), and mortality (21.9% vs. 6.9%, $p = 0.041$) (Table 5).

Table 5: Association Between CT Findings and Clinical Outcomes (n = 90)

Outcome	Abnormal CT (n=32)	Normal CT (n=58)	p-value
ICU admission	18 (56.3%)	8 (13.8%)	<0.001*
Mechanical ventilation	14 (43.8%)	4 (6.9%)	<0.001*
Neurological sequelae	11 (34.4%)	6 (10.3%)	0.006*
In-hospital mortality	7 (21.9%)	4 (6.9%)	0.041*

*Statistically significant at $p < 0.05$

Overall, lumbar puncture remained the definitive diagnostic modality, confirming meningitis in the majority of clinically suspected cases. Contrast-enhanced CT demonstrated limited sensitivity for diagnosing meningitis, but it played a critical role in identifying patients at risk of complications from lumbar puncture. Furthermore, abnormal CT findings were strongly associated with clinical severity and adverse outcomes, underscoring their value in risk stratification rather than primary diagnosis.

DISCUSSION

The mean age of patients was 34.8 ± 15.6 years, reflecting the predominance of young adults with meningitis in LMIC settings. Males constituted 56.7% of the cohort, and 61.1% were urban residents. Fever (88.9%), headache (82.2%), and neck stiffness (70.0%) were the most frequent presenting symptoms, consistent with the classical triad described by Salazar and Hasbun et al. (8,9). Altered level of consciousness was observed in 38.9% of patients, a clinically important finding given its association with poor outcomes and its role as an indication for pre-LP neuroimaging in international guidelines (8,10). Comorbidities were present in 48.9% of patients, including diabetes mellitus (20.0%) and immunocompromised states (12.2%), which are recognized risk factors for severe and atypical presentations (8,11).

A CECT of the brain was performed in all patients, with abnormalities detected in 35.6% of cases. The most frequent findings were cerebral edema (14.4%), meningeal enhancement (11.1%), hydrocephalus

(5.6%), and space-occupying lesions (4.4%). Radiological contraindications to LP were identified in 8.9% of cases. These findings align with prior reports by Nagra et al. and Machingaidze et al., who demonstrated that CT abnormalities are relatively infrequent and that true contraindications to LP are uncommon (12,13). Hendriks et al. similarly emphasized that routine imaging in the absence of neurological indications is not recommended and may delay treatment (14). Patel et al. showed that contrast enhancement adds limited incremental diagnostic value over non-contrast CT in most cases of suspected intracranial infection, with non-contrast CT demonstrating high specificity for detecting clinically relevant abnormalities (15).

Using CSF analysis as the reference standard, CECT demonstrated limited sensitivity (42.1%) but moderate specificity (83.3%) for detecting meningitis-related abnormalities, confirming that CT is a poor primary diagnostic tool for meningitis, as previously reported by Salazar et al., Hasbun et al., and Nagra et al. (8,12). In contrast, LP confirmed meningitis in 84.4% of patients, supporting its role as the definitive diagnostic modality, as emphasized by Vickers et al. and Holdgate and Cuthbert (16,17). Importantly, CECT identified all patients with contraindications to LP, supporting its selective use in patients with high-risk neurological features, in line with IDSA recommendations (8,10).

Bacterial meningitis accounted for 41.1% of cases, viral meningitis for 31.1%, and tuberculous meningitis for 12.2%, reflecting the epidemiological pattern in Pakistan and other LMICs, where tuberculosis remains endemic (6,7). Salazar and Hasbun et al. reported a similar predominance of bacterial etiologies in community-acquired meningitis. At the same time, Majed et al. documented a much lower burden of bacterial and tuberculous meningitis in high-income settings (8,18).

Post-stratification showed that CT abnormalities were significantly associated with altered consciousness, seizures, and papilledema ($p \leq 0.02$), findings consistent with those of Gulholm et al. and Salazar and Hasbun et al., who demonstrated that these neurological features are the principal clinical predictors of intracranial complications and valid indications for pre-LP imaging (8,10). Fever and neck stiffness were not associated with CT abnormalities, consistent with observations by Cortelli et al. that these cardinal symptoms do not reliably predict raised intracranial pressure (11). CT abnormalities were more frequent in bacterial meningitis than in viral or tuberculous meningitis, in line with the higher inflammatory burden described by Salazar et al., Hasbun et al., and Hendriks et al. (8,14).

Patients undergoing CT prior to LP had longer ED stays (6.2 ± 2.1 vs. 4.8 ± 1.7 hours, $p = 0.02$), consistent with delays in antibiotic administration reported by Gulholm et al. and Salazar and Hasbun et al. (8,10). Overall, in-hospital mortality was 12.2%, with ICU admission in 28.9% and mechanical ventilation in 20.0%. Abnormal CT findings were associated with significantly higher rates of ICU admission, mechanical ventilation, neurological sequelae, and mortality, supporting prior evidence that CT abnormalities reflect disease severity and adverse prognosis (8,10,13).

Collectively, these findings support the selective, guideline-concordant use of CECT brain in patients with suspected meningitis. While CT has limited diagnostic sensitivity for meningitis itself, it remains valuable for identifying contraindications to LP and stratifying disease severity. LP with CSF analysis remains the definitive diagnostic modality, and unnecessary pre-LP imaging should be avoided to minimize treatment delays, particularly in LMIC settings such as Pakistan.

CONCLUSION

In patients presenting with suspected meningitis, contrast-enhanced CT of the brain provides limited diagnostic value for confirming infection but is valuable for identifying contraindications to lumbar

puncture and for stratifying disease severity. Lumbar puncture with cerebrospinal fluid analysis remains the cornerstone of diagnosis. A selective, guideline-concordant approach to pre-LP neuroimaging may reduce unnecessary delays in antimicrobial therapy and improve clinical outcomes, particularly in resource-limited emergency care settings.

DECLARATIONS

Data Availability Statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned. (IRBEC-SHIFAIN-230-24)

Consent for publication

Approved

Funding

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

SYED AHSAN RAZA AFTAB MOHYUDDIN (Post Graduate Trainee)

Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, and final approval of manuscript.

Manuscript drafting.

MUHAMMAD FAIZAN HAMID (MO)

Data entry, data analysis, and drafting an article.

MUHAMMAD IMRAN KHAN (MO)

Manuscript revisions, critical input.

AYESHA AKRAM (Post Graduate Trainee)

Study Design, Review of Literature

SYEDA SOBYA OWAIS (Consultant)

Conception of Study, Final approval of manuscript.

REFERENCES

1. Bewersdorf J., Grandgirard D., Koedel U., & Leib S. Novel and preclinical treatment strategies in pneumococcal meningitis. *Current Opinion in Infectious Diseases* 2018;31(1):85-92. <https://doi.org/10.1097/qco.0000000000000416>
2. Beckham J. and Tyler K. Neuro-Intensive Care of Patients with Acute CNS Infections. *Neurotherapeutics* 2012;9(1):124-138. <https://doi.org/10.1007/s13311-011-0086-5>
3. Gulholm T., Kim M., Lennard K., Mirdad F., Overton K., Martinello M. et al. Clinical variation in the early assessment and management of suspected community-acquired meningitis: a multicentre retrospective study. *Internal Medicine Journal* 2023;53(12):2298-2306. <https://doi.org/10.1111/imj.16076>
4. Patel J., Jenson M., Hernández M., Fiester P., & Rao D. Is Contrast-Enhanced Computed Tomography Redundant for Suspected Intracranial Infection in the Emergency Setting?. *Journal of Computer Assisted Tomography* 2022;47(1):102-107. <https://doi.org/10.1097/rct.0000000000001392>

5. Brouwer M. and Beek D. Viral meningitis in the UK: time to speed up. *The Lancet Infectious Diseases* 2018;18(9):930-931. [https://doi.org/10.1016/s1473-3099\(18\)30287-1](https://doi.org/10.1016/s1473-3099(18)30287-1)
6. Zafar Z., Hafeez M., & Butt M. Elusive tuberculous meningitis with rare neurological complication of longitudinally extensive transverse myelitis: a case report. *Spinal Cord Series and Cases* 2021;7(1). <https://doi.org/10.1038/s41394-021-00445-y>
7. Zandvakili A., Kobayashi T., Kaewpoowat Q., Parsons M., Ford B., Barker J. et al. Pelvic and central nervous system tuberculosis complicated by a paradoxical response manifesting as a spinal tuberculoma: a case report. *BMC Infectious Diseases* 2022;22(1). <https://doi.org/10.1186/s12879-022-07731-6>
8. Salazar L. and Hasbun R. Cranial Imaging Before Lumbar Puncture in Adults With Community-Acquired Meningitis: Clinical Utility and Adherence to the Infectious Diseases Society of America Guidelines. *Clinical Infectious Diseases* 2017;64(12):1657-1662. <https://doi.org/10.1093/cid/cix240>
9. Mateen F. and Mohr D. 45-Year-Old Woman With Recurrent Headache and Photophobia. *Mayo Clinic Proceedings* 2008;83(8):951-954. [https://doi.org/10.1016/s0025-6196\(11\)60772-6](https://doi.org/10.1016/s0025-6196(11)60772-6)
10. Gulholm T., Kim M., Lennard K., Mirdad F., Overton K., Martinello M. et al. Clinical variation in the early assessment and management of suspected community-acquired meningitis: a multicentre retrospective study. *Internal Medicine Journal* 2023;53(12):2298-2306. <https://doi.org/10.1111/imj.16076>
11. Cortelli P., Cevoli S., Nonino F., Baronciani D., Magrini N., Re G., et al. Evidence-Based Diagnosis of Nontraumatic Headache in the Emergency Department: A Consensus Statement on Four Clinical Scenarios. *Headache, the Journal of Head and Face Pain* 2004;44(6):587-595. <https://doi.org/10.1111/j.1526-4610.2004.446007.x>
12. Nagra I., Wee B., Short J., & Banerjee A. The role of cranial CT in the investigation of meningitis. *JRSM Short Reports* 2011;2(3):1-9. <https://doi.org/10.1258/shorts.2011.010113>
13. Machingaidze P., Buys H., Kilborn T., & Muloiswa R. Clinical use and indications for head computed tomography in children presenting with acute medical illness in a low- and middle-income setting. *Plos One* 2020;15(9):e0239731. <https://doi.org/10.1371/journal.pone.0239731>
14. Hendriks T., Kirsch C., Gibson D., & Kuthubutheen J. Temporal Bone Skull Base Defects—The Value and Importance of Early Detection to Prevent Late Costly Morbidity and Mortality. *Journal of Neurological Surgery Part B Skull Base* 2022;83(06):653-662. <https://doi.org/10.1055/a-1933-3958>
15. Patel J., Jenson M., Hernández M., Fiester P., & Rao D. Is Contrast-Enhanced Computed Tomography Redundant for Suspected Intracranial Infection in the Emergency Setting?. *Journal of Computer Assisted Tomography* 2022;47(1):102-107. <https://doi.org/10.1097/rct.0000000000001392>
16. Holdgate A. and Cuthbert K. Perils and pitfalls of lumbar puncture in the emergency department. *Emergency Medicine* 2001;13(3):351-358. <https://doi.org/10.1046/j.1035-6851.2001.00239.x>
17. Vickers A., Donnelly J., Moore J., Barnum S., Schein T., & Wang H. Epidemiology of lumbar punctures in hospitalized patients in the United States. *Plos One* 2018;13(12):e0208622. <https://doi.org/10.1371/journal.pone.0208622>
18. Majed B., Zéphir H., Pichonnier-Cassagne V., Yazdanpanah Y., Lestavel P., Valette P., et al. Lumbar punctures: use and diagnostic efficiency in emergency medical departments. *International Journal of Emergency Medicine* 2009;2(4):227-235. <https://doi.org/10.1007/s12245-009-0128-5>



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons licence unless indicated otherwise in a credit line to the material. Suppose material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use. In that case, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. © The Author(s) 2025