BRIEF REPORT

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Diagnostic clues for differentiating Merkel cell carcinoma from lymphoma in fine-needle aspiration cytology

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Abstract

Nodal fine needle aspiration (FNA) is usually the first procedure in the work-up of malignancy of unknown primary. Merkel cell carcinoma (MCC) is an aggressive cutaneous cancer more common in Caucasians but rare among Asians. It is a diagnostic challenge in evaluating FNA from a metastatic MCC without the knowledge of a current or prior history of skin cancer. We report the case of a Taiwanese male with cervical and axillary masses. The diagnosis of the FNA from the axillary lymph node was lymphoproliferative lesion suspicious for lymphoma. The histopathological evaluation of nodal biopsy revealed a metastatic neuroendocrine carcinoma and the subsequent excision of the right palm tumor confirmed MCC. Retrospective review of the FNA and imprint cytology smears of the nodal biopsy showed nuclear molding, Indian filing and rare cytoplasmic pale bodies, but no lymphoglandular bodies. Cytologically metastatic MCC may mimic small round cell tumor including lymphoma, we consider these three cytological features as additional diagnostic clues for metastatic MCC. In this report, we present the cytologic and pathological features of this metastatic MCC and discuss the differential diagnosis of the cytologic mimickers.

KEYWORDS
cytoplasmic pale body, fine-needle aspiration cytology, Indian filing, Merkel cell carcinoma, nuclear molding

1 | INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine carcinoma, and mainly affects individuals with long-term sun exposure or specific epidemiological factors.[1–4] Diagnosis of stage IV MCC is associated with only an approximate 11% survival and a median survival of 6 months.[4] Therefore, early definitive diagnosis of metastatic MCC allows for accurate staging and prompt, appropriate management.

Fine-needle aspiration cytology (FNA) of small round cell tumors can be diagnostically challenging.[5,6] In the literature, most published studies of the cytologic findings of MCC are single case reports or small series.[7–16] As the cytomorphology of MCC may mimic other malignancies, particularly lymphoma and pulmonary small cell carcinoma (SmCC),[7,9,10,12–14] immunocytochemistry is useful in confirming the diagnosis. Herein we report a unique case of MCC with metastatic nodal diseases, in which the FNA smear showed nuclear molding, Indian filing, and cytoplasmic pale bodies. We consider these findings as diagnostic clues for differentiating MCC from lymphoma. In this report, we emphasize the cytological features and discuss the potential diagnostic pitfalls posed by metastatic MCC in FNA specimens.

2 | CASE REPORT

2.1 | Clinical history and disease course

A 63-year-old Taiwanese male, a long-term resident in a psychiatric hospital, presented with a skin lesion in his right palm in March 2012.

Skin biopsy at that time showed only necrotic tissue. Four years later, he presented with right cervical lymphadenopathy. CT scans revealed confluent lymphadenopathy in the right cervical, supraclavicular, and axillary nodes. FNA from the right axillary nodes was performed, and the cytologic diagnosis was lymphoproliferative lesion suspicious for lymphoma. Subsequent incisional biopsy of the lymph node was diagnosed as metastatic neuroendocrine carcinoma. In June 2016, MCC was proved by excisional biopsy of the skin lesion in the right palm. After the confirmation of MCC with multiple organ metastases, he was put under hospice care and passed away in August 2016.

2.2 | Cytological and pathological features

The cytopathologic features of the lymph node FNA showed highly cellular smears with single and cohesive clusters of small to intermediate-sized cells (Figure 1). The cells had high N/C ratio with scant cytoplasm. The nuclei were relatively uniform in shape, with indistinct nucleoli. Nuclear molding and an "Indian" filing pattern were also observed (Figure 1).

The imprint cytology from lymph node biopsy yielded abundant monotonous tumor cells, resembling dispersed cell pattern of non-Hodgkin lymphoma (NHL) (Figure 1). Liu stain (a Romanowsky-type stain) showed the presence of nuclear molding and cohesive cell clusters. There were no lymphoglandular bodies. The hematoxylin–eosin (H&E) section of lymph node displayed solid nests of hyperchromatic tumor cells. Immunohistochemically, the tumor cells

expressed CD56, but not CD3 or CD20, confirming the diagnosis of neuroendocrine carcinoma.

Figure 2 depicts the clinical picture of skin lesion, showing an erythematous nodule with abundant crusts in the right palm. The dermal-based tumor consisted of small blue cells arranged in solid sheets or nests. Immunohistochemically, these tumor cells expressed CK20 and cytokeratin AE1/AE3, both in a perinuclear dot-like staining pattern. They also expressed CD56, synaptophysin, and chromogranin A. Furthermore, the neoplastic cells were positive for Merkel cell polyoma virus using clone CM2B4 (Santa Cruz Biotechnology). Combining the clinical and pathological findings together, a diagnosis of MCC with nodal metastasis was rendered.

3 | DISCUSSION

In a review of 69 MCC cases sampled by FNA, the common cytologic feature of MCC was dispersed cell pattern, with at least some cohesive groups of cells.[7] The small cell groups were composed of tightly packed, molded nuclei with little or no cytoplasm. The nuclei showed mild to moderate anisokaryosis, stippled chromatin, and inconspicuous nucleoli.[7] In our current case, we noted that some neoplastic cells were cohesive and molded together in single cellular files, or Indian filing, which has been described only once in the English literature in a case report.[14] Furthermore, cytoplasmic pale bodies, or so-called "intermediate filament buttons/bodies" were also identified in the cytoplasm, supporting the diagnosis of MCC, with confirmation from immunocytochemistry.[8,14,16,17]
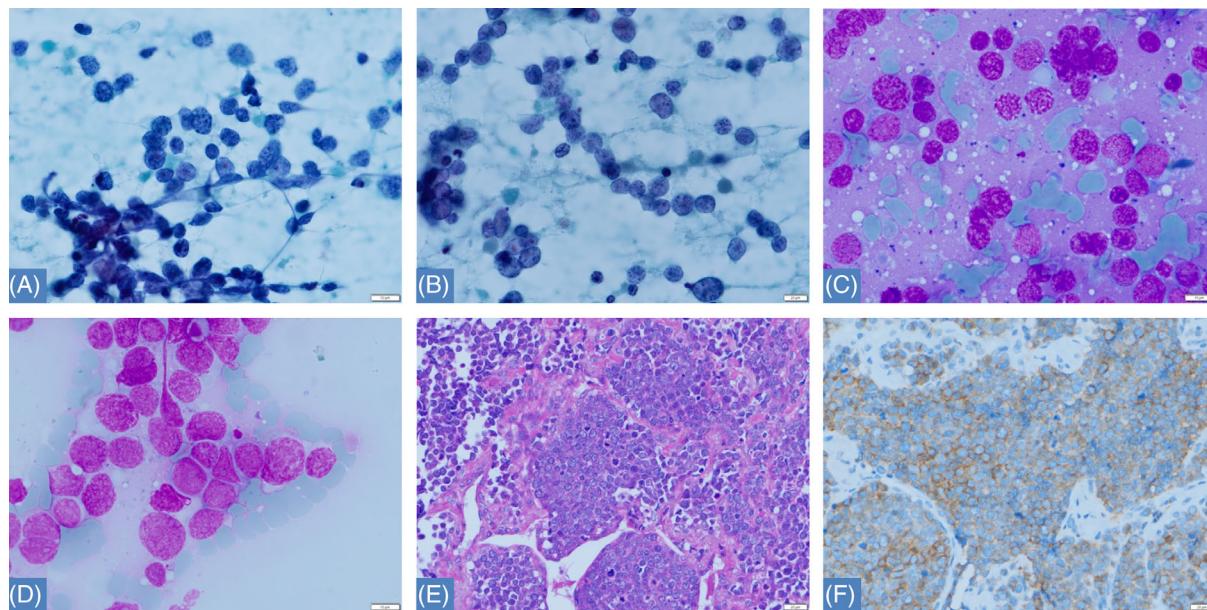

FIGURE 1 (A) and (B) Representative photos of the fine-needle aspiration (FNA) cytology of the axillary lymph node with Papanicolaou stain. The tumor cell nuclei are mostly round-shaped with a mild degree of size variation, a fine chromatin pattern, and with a small nucleolus in some cells. Loosely cohesive neoplastic cells show nuclear molding and an "Indian" filing pattern (magnification ×1000). (C)–(F) Incisional biopsy of the right axillary lymph node. (C) and (D) Imprint cytology showing monotonous neoplastic cells admixed with some small lymphocytes and nuclear molding (Liu stain, ×1000). (E) Hematoxylin–eosin (H&E) stain shows solid nests of monotonous neoplastic cells with fine chromatin and frequent mitoses. (F) Immunohistochemically, the neoplastic cells express CD56, but not CD3 or CD20 (now shown), confirming neuroendocrine origin of this nodal metastasis (E and F, ×400)
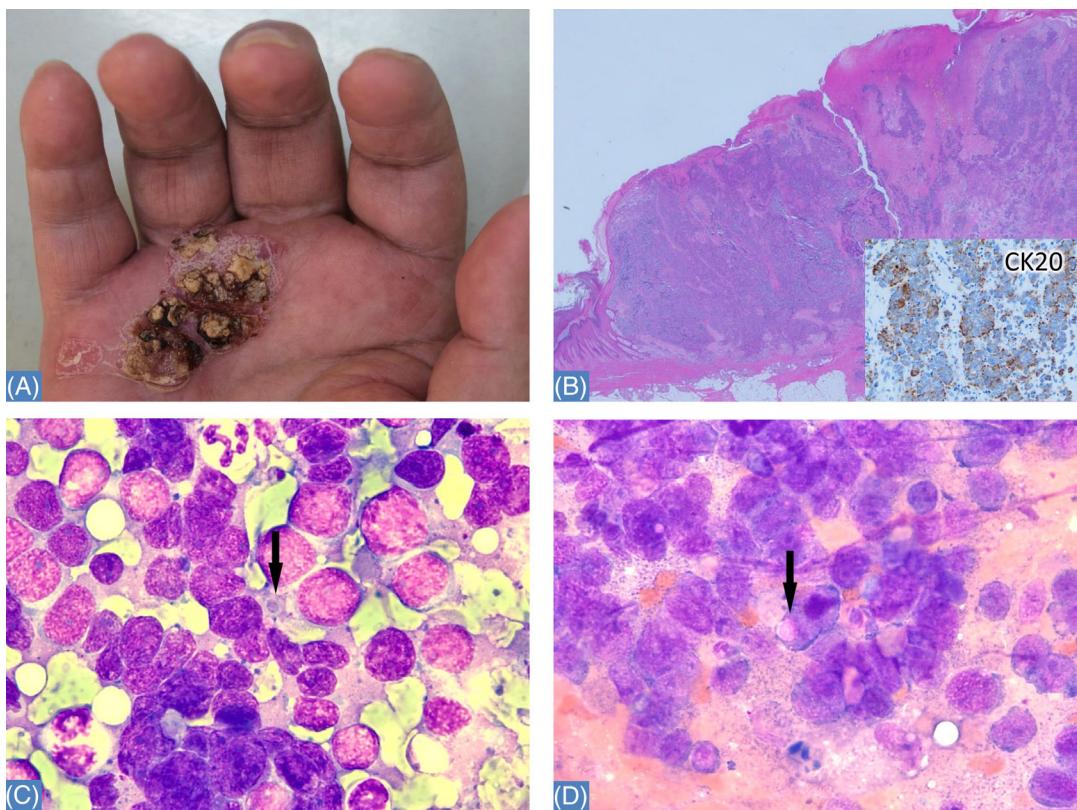
FIGURE 2 (A) An exophytic and erythematous skin tumor with abundant crusts in the right palm. (B) Scanning view shows an exophytic dermal tumor with surface ulceration (×12.5); the neoplastic cells express CK20 in a perinuclear dot-like pattern (inset, ×400). They also expressed cytokeratin AE1/AE3, CD56, synaptophysin, and chromogranin A (not shown), confirming the diagnosis of Merkel cell carcinoma. In this current case, occasional cytoplasmic pale bodies (arrows) are identified in the tumor cells (C, imprint cytology; D, fine-needle aspiration [FNA] cytology of metastatic node. Liu stain, ×1000)

The differential diagnoses of MCC center mainly on so-called small round cell tumors.[7,9,12] NHL pose the most common differential diagnosis for MCC as exemplified in the initial cytological diagnosis in our case and many other reports in the literature.[7,9,12,18] The main cytologic features of MCC include small cohesive groups and occasional pseudorosette formation.[7,13,14,19] In contrast, lymphocytes are individually dispersed without tissue fragments.[20] Among NHL, the most common type is diffuse large B-cell lymphoma, in which the neoplastic cells are large and dyscohesive, with lymphoglandular bodies in the background. The nuclei are vesicular, usually with irregular nuclear contours, a coarse chromatin pattern, either with or without a single prominent nucleolus.[10] Lymphoma or leukemia of blastic type (such as lymphoblastic lymphoma [LBL] or blastic mantle cell lymphoma) may mimic the fine chromatin pattern in MCC. LBL shows small to medium-sized lymphoid cells with either round or highly irregular-shaped nuclei. The chromatin pattern is very fine and blast-like, and numerous mitoses are usually found.[21] The blastic variant of mantle cell lymphoma exhibits intermediate to large cells with slightly irregular nuclear contours and evenly distributed chromatin, frequently confused with LBL.[22] Lymphoglandular bodies are valuable in alerting the (cyto)pathologists to the possibility of NHL.[5,19] We demonstrate that presence of nuclear molding, Indian filing, and absence of lymphoglandular bodies are the diagnostic features of MCC.[19] In cases suspicious for lymphoma, ancillary studies such as immunocytochemistry, flow cytometric immunophenotyping, and clonality assay may help differentiating lymphoma from MCC.[10]

SmCC share similar cytomorphologic features with MCC as depicted in Figures 1 and 2. Paranuclear blue inclusions have been described as features of SmCC in Romanowsky-stained smears.[20,23,24] Other than SmCC, these paranuclear blue bodies have also been identified in MCC cells.[25] On the other hand, cytoplasmic pale bodies were occasionally found when the smears were carefully scrutinized (Figure 2C,D). These inclusions were usually ovoid or crescent-shaped, located close to the nucleus and occasionally indented it.[8,17] Such paranuclear inclusions were mostly seen in Romanowsky or H&E stained smears.[7,8,13] Ultrastructurally, MCC cells contain whorls of perinuclear intermediate filaments, which represent the equivalent of the "buttons" seen by light microscopy.[11,17] Theses cytoplasmic pale bodies or so-called "intermediate filament bodies" have not been reported in SmCC yet and may serve as an additional differential diagnostic feature between these two tumors.[8]

Differentiating MCC from its mimics, especially in metastatic lesions, requires the use of a comprehensive immunocytochemical work-up. MCC cells typically express both epithelial and neuroendocrine markers.[26,27] CK20 is typically positive, often in a perinuclear dot-like pattern, but rarely in pulmonary SmCC.[28] The other markers useful for differential diagnosis are CK7 and TTF-1, both are usually positive

in SmCC of lung but negative in MCC.[10,11] Most MCC cases were associated with Merkel cell polyoma virus, which could be identified by immunohistochemical study with clone CM2B4.[29–31] A positive finding would be helpful for supporting the diagnosis of MCC as in our case.

4 | CONCLUSION

Although rare, MCC should be considered as a diagnostic possibility in the FNA evaluation of metastatic malignancy with an unknown primary and a small round cell cytomorphology. MCC is easily mistaken for NHL and metastatic SmCC. In this report, we showed that the identification of cohesive cell clusters with nuclear molding, Indian filing, paranuclear blue inclusions or cytoplasmic pale bodies can facilitate the distinction between MCC and NHL. As there are many mimickers of MCC, we need a large panel of immunocytochemical antibodies in conjunction with clinical and radiologic findings to reach a correct diagnosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Investigated the case: Chih-Yi Liu, Feng-Jie Lai, Sheng-Tsung Chang, and Shih-Sung Chuang. *Wrote the manuscript*: Chih-Yi Liu and Shih-Sung Chuang. *Approved the manuscript*: Chih-Yi Liu, Feng-Jie Lai, Sheng-Tsung Chang, and Shih-Sung Chuang.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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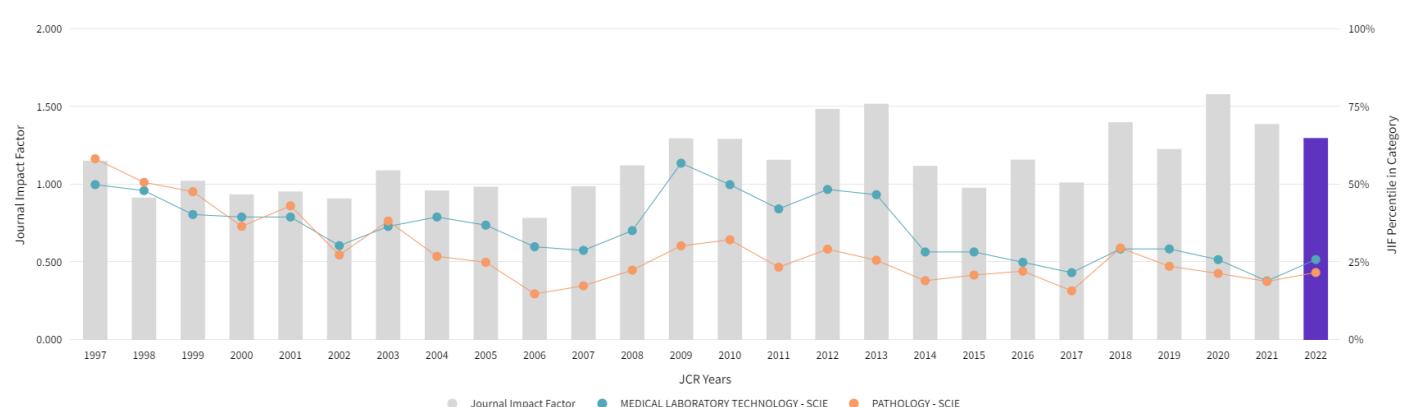
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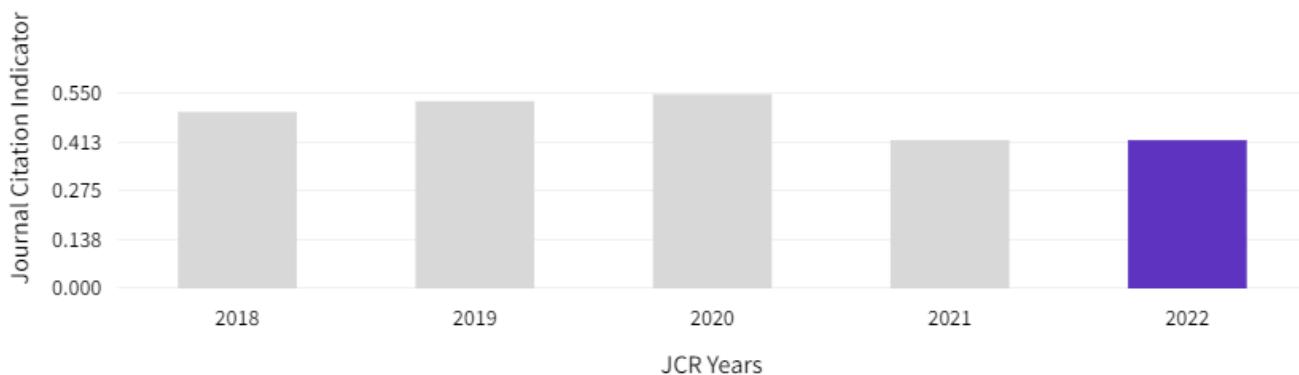
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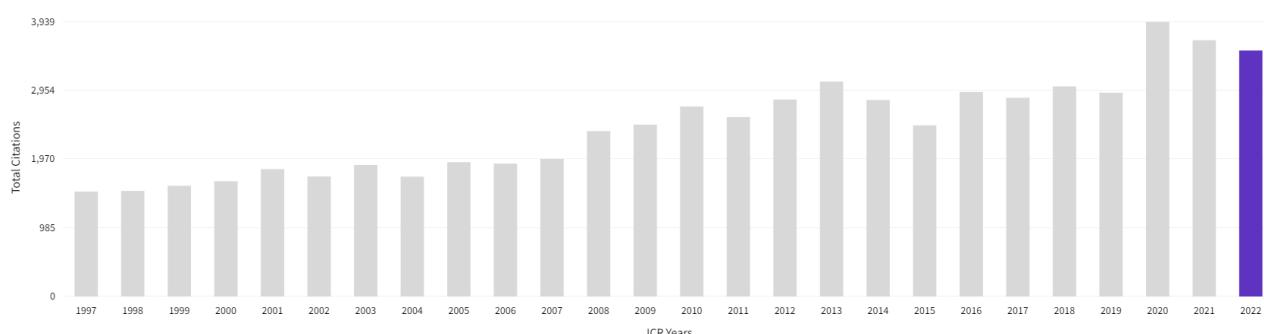
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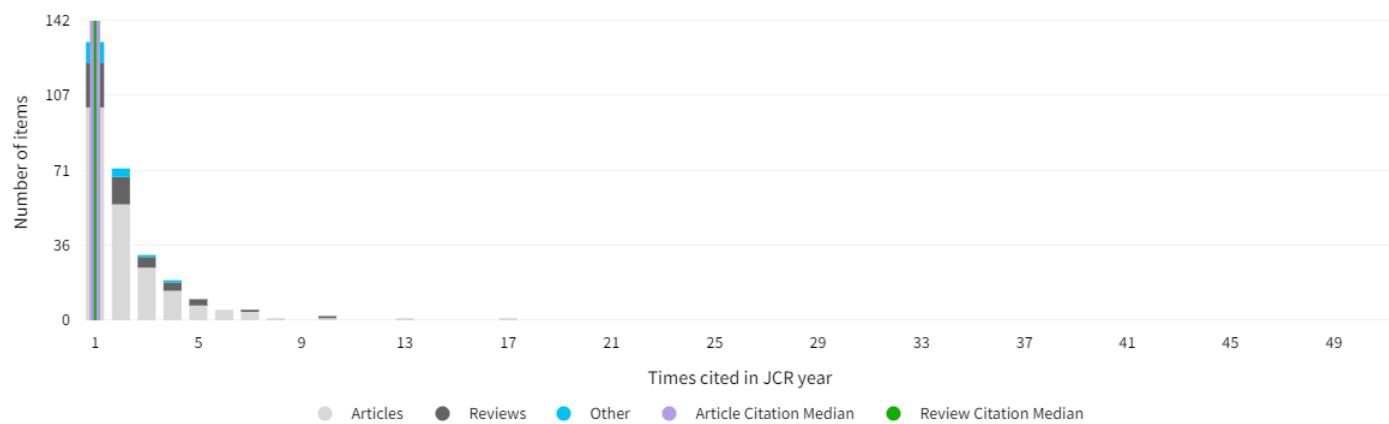
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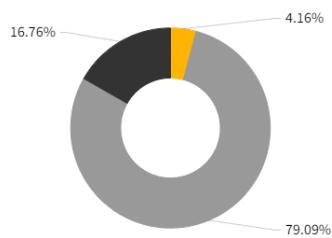
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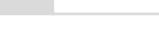
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2018	21/29	Q3	29.31	
2017	24/30	Q4	21.67	
2016	23/30	Q4	25.00	
2015	22/30	Q3	28.33	
2014	22/30	Q3	28.33	
2013	17/31	Q3	46.77	
2012	17/32	Q3	48.44	
2011	19/32	Q3	42.19	
2010	16/31	Q3	50.00	
2009	13/29	Q2	56.90	
2008	18/27	Q3	35.19	
2007	19/26	Q3	28.85	
2006	18/25	Q3	30.00	
2005	15/23	Q3	36.96	
2004	15/24	Q3	39.58	
2003	17/26	Q3	36.54	
2002	20/28	Q3	30.36	
2001	15/24	Q3	39.58	
2000	15/24	Q3	39.58	
1999	16/26	Q3	40.38	
1998	14/26	Q3	48.08	
1997	11/21	Q3	50.00	

60/76

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2021	63/77	Q4	18.83	
2020	61/77	Q4	21.43	
2019	60/78	Q4	23.72	
2018	54/76	Q3	29.61	
2017	67/79	Q4	15.82	
2016	62/79	Q4	22.15	
2015	63/79	Q4	20.89	
2014	62/76	Q4	19.08	
2013	57/76	Q3	25.66	
2012	55/77	Q3	29.22	
2011	61/79	Q4	23.42	
2010	52/76	Q3	32.24	
2009	50/71	Q3	30.28	
2008	54/69	Q4	22.46	
2007	55/66	Q4	17.42	
2006	55/64	Q4	14.84	
2005	50/66	Q4	25.00	
2004	48/65	Q3	26.92	
2003	40/64	Q3	38.28	
2002	47/64	Q3	27.34	
2001	38/66	Q3	43.18	
2000	43/67	Q3	36.57	
1999	35/66	Q3	47.73	
1998	34/68	Q2	50.74	
1997	28/66	Q2	58.33	

Rank by Journal Citation Indicator (JCI)

Journals within a category are sorted in descending order by Journal Citation Indicator (JCI) resulting in the Category Ranking below. A separate rank is shown for each category in which the journal is listed in JCR. Data for the most recent year is presented at the top of the list, with other years shown in reverse chronological order.Learn more

JCR YEAR	JCI RANK	QUARTILE	JCI PERCENTILE	JCR YEAR	JCI RANK	QUARTILE	JCI PERCENTILE
2022	25/32	Q4	23.44	2022	62/86	Q3	28.49
2021	25/33	Q4	25.76	2021	65/89	Q3	27.53
2020	21/33	Q3	37.88	2020	55/90	Q3	39.44
2019	21/33	Q3	37.88	2019	59/89	Q3	34.27
2018	20/32	Q3	39.06	2018	61/89	Q3	32.02
2017	20/31	Q3	37.10	2017	59/88	Q3	33.52

Citation network

Cited Half-life

9.1 years

The Cited Half-Life is the median age of the items in this journal that were cited in the JCR year. Half of a journal's cited items were published more recently than the cited half-life.

TOTAL NUMBER OF CITES
3,528

NON-SELF CITATIONS
3,180

SELF CITATIONS
348

Cited Years (y-axis): 2022, 2021, 2020, 2019, 2018, 2017, 2016, 2015, 2014, 2013
Number of Cites (x-axis): 0, 50, 100, 150, 200, 250, 300, 350, 400

- Non-self citations: citations to the journal from the items in other sources
- Citations to items in the journal from items in the same journal
- Citations used to calculate the Impact Factor

	# OF CITES FROM 2022	CUMULATIVE %	# OF CITING SOURCES
	3,528 citations	**100.00%**	**729 sources**
	37 citations	1.05%	19 sources
	174 citations	5.98%	75 sources
	444 citations	18.57%	176 sources
	276 citations	26.39%	127 sources
	170 citations	31.21%	96 sources
	180 citations	36.31%	92 sources
	181 citations	41.44%	110 sources
	133 citations	45.21%	83 sources
	160 citations	49.74%	90 sources
	128 citations	53.37%	80 sources

Previous years:
1,645 citations