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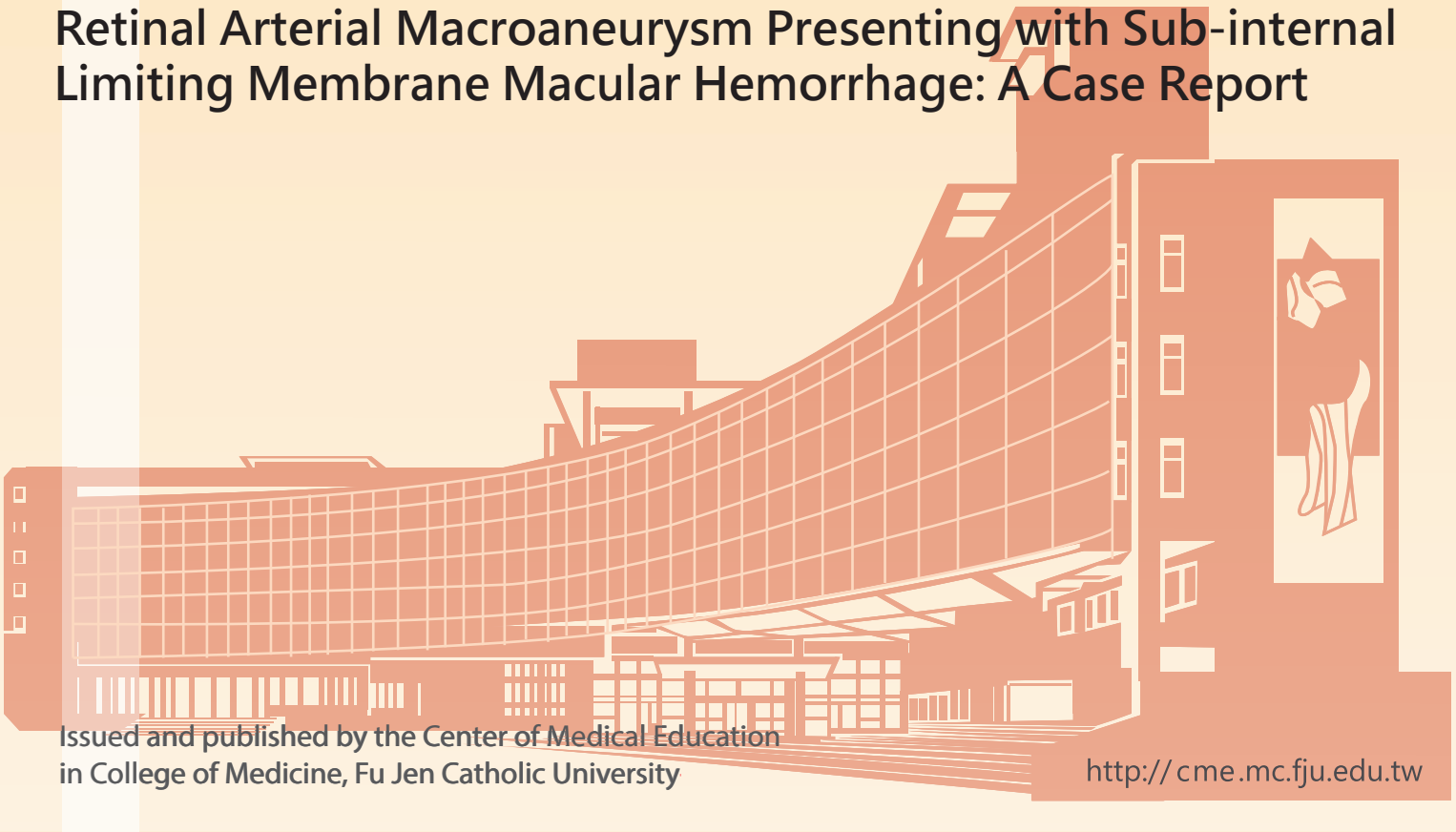
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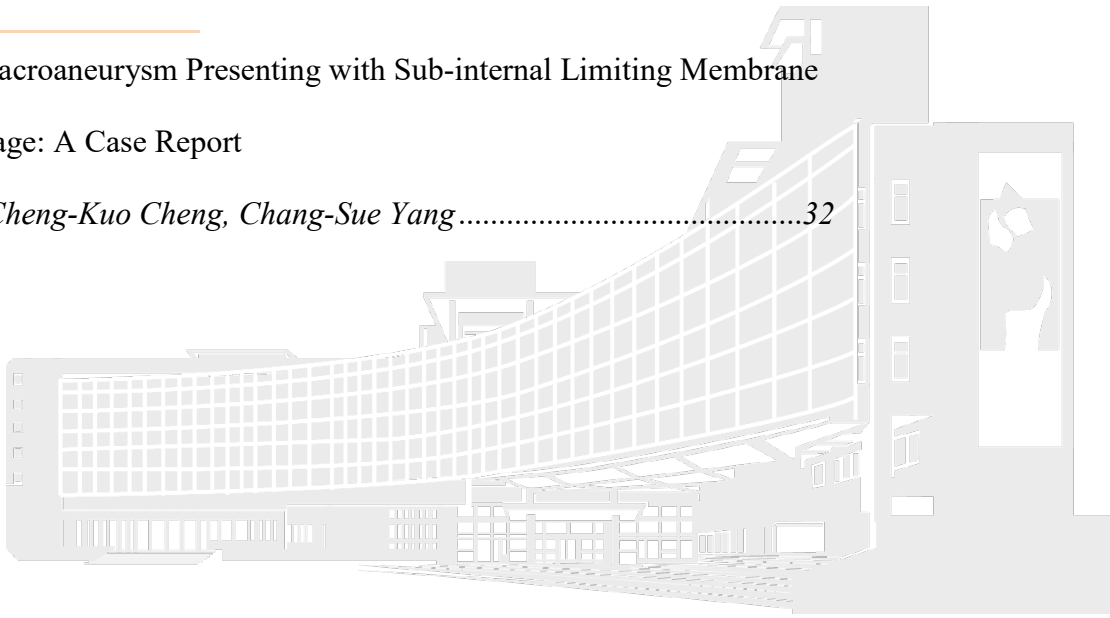
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Original Research Article

Diagnostic accuracy of serum IgG4 for IgG4-related disease: A meta-analysis

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ABSTRACT

Background: Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immune-mediated fibro-inflammatory condition with the potential to affect multiple organ systems. The clinical presentation of IgG4-RD is frequently nonspecific and can resemble that of malignancies. A misdiagnosis could lead to unnecessary surgery. Serum IgG4 serves as a serological biomarker for the disease. The clinical applicability of serum IgG4, however, remains a subject of ongoing investigation. The objective of the meta-analysis is to re-evaluate the efficacy of serum IgG4 for the detection of IgG4-RD. ***Materials and methods:*** A literature search was conducted in the PubMed, Embase, and Cochrane Library databases to identify eligible articles. Studies that included patients with suspected or confirmed IgG4-RD were included. A reference standard, in the form of histopathology, was utilized for confirmation. Furthermore, studies that provided sufficient data for conducting a meta-analysis were assessed. The meta-analysis was performed using a bivariate random-effects model. ***Results:*** A total of 20 papers comprising 11,650 patients were included in the study. The meta-analysis yielded a pooled sensitivity of 88.2% and a pooled specificity of 80.5% of serum IgG4 for identifying IgG4-RD. A subgroup analysis of participants with suspected IgG4-related Sclerosing Cholangitis (IgG4-SC) demonstrated a sensitivity of 76.2% and a specificity of 97.4%. The utilization of a 135 mg/dL cut-off in manuscripts yielded a pooled sensitivity of 87.9%. ***Conclusion:*** This meta-analysis validated that serum IgG4 serves as an accuracy tool for the initial evaluation of patients with suspected IgG4-RD. Another potential benefit of this biomarker is its specificity to IgG4-SC.

Keywords: Immunoglobulin G4-Related Disease, Serum IgG4, Meta-analysis, Sensitivity and



Specificity

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immune-mediated fibro-inflammatory condition capable of affecting multiple organ systems[1] . Since its initial recognition as a unified entity linking autoimmune pancreatitis (AIP) to other organ manifestations, the clinical understanding of IgG4-RD has expanded rapidly[2]. The disease is characterized histologically by dense lymphoplasmacytic infiltration rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis[1]. While the pancreas remains the most frequently studied organ, manifestations in the bile ducts (IgG4-related sclerosing cholangitis), salivary glands (Mikulicz's disease), retroperitoneum (retroperitoneal fibrosis), and kidneys are increasingly recognized[1,3].

The diagnosis of IgG4-RD remains a significant clinical challenge. The clinical presentation is often nonspecific and can mimic malignancies, such as pancreatobiliary cancer, lymphoma, or other autoimmune conditions like Sjögren's syndrome and primary sclerosing cholangitis (PSC)[3-5]. Delayed diagnosis can lead to unnecessary surgical interventions—such as pancreaticoduodenectomy for presumed cancer[3]. Consequently, accurate, non-invasive diagnostic tools are critical for distinguishing IgG4-RD from its mimics.

Currently, the gold standard for diagnosis relies on the 2020 revised comprehensive diagnostic criteria, which integrate serology, imaging features, and, crucially, histopathological confirmation[6]. However, obtaining biopsy specimens can be invasive, particularly for retroperitoneal or deep pancreatic lesions[7]. Furthermore, biopsy samples obtained via fine-needle aspiration may yield insufficient tissue to evaluate storiform fibrosis or obliterative phlebitis[8].

Serum IgG4 levels serve as the primary serological biomarker for the disease[6]. Clinically, a cut-off value of >135 mg/dL has been widely utilized to distinguish IgG4-RD from other conditions[6]. However, the diagnostic utility of serum IgG4 is a subject of ongoing debate. While elevated serum IgG4 is a hallmark of the disease, it is not pathognomonic; serum IgG4 elevations are frequently observed in pancreato-biliary disease, connective tissue disease, recurrent pneumonia, and immunodeficiency, leading to concerns regarding false positives[9]. Conversely, a minor proportion of histologically confirmed IgG4-RD patients present with normal serum IgG4 levels, which has led to concerns regarding the potential for false negative results[9].

In light of these discrepancies and the growing body of recent studies, there is an urgent need to re-evaluate the diagnostic performance of serum IgG4. A previous meta-analysis has addressed this topic. However, given the significant heterogeneity in study design, inclusion criteria, and patient groups, there is a need for an updated synthesis[10]. This study aims to perform a diagnostic meta-analysis of the available literature to determine the overall diagnostic accuracy (sensitivity and specificity) of serum IgG4 for detecting IgG4-RD and to investigate potential sources of heterogeneity through subgroup analysis and meta-regression.

MATERIALS AND METHODS

Study design and registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) guidelines[11]. The present study has been duly registered within the PROSPERO database. (registration number: CRD420261288967).

Search strategy and selection criteria

A comprehensive literature search was conducted to identify studies published up to 2025. A systematic literature search was performed in the PubMed, Embase, and Cochrane Library databases to obtain potentially relevant studies. The following terminology was employed: (Immunoglobulin G4-Related Disease or IgG4-related disease or IgG4-RD) and serum IgG4 and (Diagnostic Accuracy or sensitivity or specificity). In order to maximize the comprehensiveness of the search, a combination of Medical Subject Headings and free texts was incorporated into the search strings. Studies were included if they met the following criteria: (1) The study design was prospective or retrospective; (2) The study population included patients with suspected or confirmed IgG4-RD; (3) Serum IgG4 was used as the index test; (4) A reference standard (histopathology) was used for confirmation; (5) Sufficient data were available to construct a 2x2 contingency table (True Positives [TP], False Positives [FP], False Negatives [FN], True Negatives [TN]); (6) English language papers were involved. Exclusion criteria included review articles, case report, case series, proposals, protocols, conference abstract, conference paper, in-house test, and pre-prints articles. A final literature search was conducted on January 5, 2026.



This search aimed to integrate the latest available publications into the study. One of the authors initially evaluated the titles and abstracts to identify potentially eligible studies for inclusion. Then, two authors independently evaluated all full-text articles that met the predetermined eligibility criteria.

Data extraction and quality assessment

Data were extracted from eligible studies. We implemented a bivariate random-effects model on a per-sample basis to conduct a meta-analysis, thereby yielding summary estimates of sensitivity and specificity. To determine the overall diagnostic value of oral cytology for oral cancer, the summary receiver operating characteristic curve was plotted[12]. The following variables were retrieved: first author, year of publication, study design (prospective/retrospective), number of participants, mean/median age, participant population (e.g., suspected IgG4-RD, biliary strictures), index test details (assay method, cut-off values), affected organs, and the reference standard used.

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool[13]. This tool evaluates four domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing. Each domain was rated as having "Low," "High," or "Unclear" risk of bias and applicability concerns.

Statistical analysis

The primary outcome measures were sensitivity and specificity. Based on the extracted TP, FP, FN, and TN values, we calculated the pooled estimates with 95% confidence intervals (CI). We utilized a bivariate random-effects model to a on a per-patient basis to conduct a meta-analysis.

Heterogeneity was explored using subgroup analyses based on:

1. Study Design: Prospective vs. Retrospective.

2. Participant Population: Patients with suspected IgG4-related sclerosing cholangitis and patients with elevated IgG4.

3. Cut-off Values: Specifically analyzing the standard cutoff of 135 mg/dL.

4. Detection Technique: Immunonephelometry methods.

Meta-regression analyses were performed. These analyses were used to quantitatively assess the impact of covariates. Covariates refers to study design, specific disease subsets, and patients with elevated IgG4 on serology. These covariates may affect the relative diagnostic accuracy. All analyses were performed using RevMan version 5.4, and MetaDiSc version 2.0[14]. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 20 studies comprising 11,650 participants were included in the final analysis[9,15-33]. As illustrated in Figure 1, the process of conducting the literature search is delineated in detailed fashion. The studies ranged in publication year from 2009 (Tabata et al.) to 2025 (Kunlayawutipong et al.; Hu et al.), reflecting the enduring interest and evolving understanding of this biomarker. The majority of studies (n=18) employed a retrospective design, while two were prospective (Su 2015; Yamamoto 2012). The sample sizes varied significantly, from smaller cohorts like Kogami 2023 (n=50) to large-scale analyses such as Yu 2015 (n=2,901). A number of studies have focused on specific manifestations, including biliary strictures (Kunlayawutipong 2025, Park 2022), retroperitoneal fibrosis (Hu 2025), and kidney disease (Saeki 2021). Conversely, other studies have enrolled more extensive populations of individuals suspected to have IgG4-RD. Immunonephelometry was the dominant detection technique (e.g., Siemens BN II). The most frequently utilized cut-off value for serum IgG4 was 135 mg/dL (used in 12 studies), though some studies utilized higher cut-offs (e.g., Ngwa 2014 used 240–280 mg/dL; Kunlayawutipong 2025 used 540 mg/dL for bile duct specificity). Table 1 presents an overview of the key characteristics of the included studies.

Meta-analysis

The meta-analysis yielded a pooled sensitivity of 88.2% (95% CI: 80.3% to 93.2%) and a pooled specificity of 80.5% (95% CI: 57% to 92.8%) of serum IgG4 for identifying IgG4-RD (Figure 2). Figures 3 and 4 present the sensitivity, specificity, and statistic values of serum IgG4, respectively, as reported in the included articles.

Quality of studies

In the domain of patient selection, the majority of studies have exhibited a low risk of bias. However, However, two studies (Ngwa 2014 and Ryu 2012) were identified as potentially exhibiting high risk of bias. This discrepancy can be attributed, at least in part, to the inclusion of patients with elevated serum IgG4, which introduces spectrum bias by excluding seronegative IgG4-RD patients. The domain of the index test demonstrated an overall low risk of bias across all studies, as serum IgG4 levels are considered objective laboratory measures that are typically unaffected by the final diagnosis during processing. The reference



standard domain exhibited unclear risk of bias in all studies. This is frequently attributable to the challenge of obtaining definitive histopathology diagnoses, or the reliance on clinical criteria when performing biopsies is not feasible in clinical settings. In the flow and timing domain, concerns were identified in five studies. These concerns potentially stemmed from partial verification in three of the studies. The subsequent two studies indicated that the analysis did not encompass all patients. Figure 5 depicts the risk of bias in each study. Figure 6 presents the overall quality of the included studies.

Subgroup analysis

In order to investigate the sources of heterogeneity, a series of subgroup analyses were conducted. Two studies that employed a prospective study design demonstrated superior performance, with a pooled sensitivity of 96.5% and specificity of 94.4%. In contrast, eighteen retrospective studies exhibited lower pooled sensitivity at 87.1% and specificity at 77.4%. Studies that enrolled participants with suspected IgG4-related Sclerosing Cholangitis (IgG4-SC) demonstrated a sensitivity of 76.2% and a specificity of 97.4%. This finding suggests that, within the specific context of biliary strictures, IgG4 may exhibit higher specificity but reduced sensitivity. The utilization of a 135 mg/dL cut-off in manuscripts yielded a pooled sensitivity of 87.9% and a pooled specificity of 81%. Table 2 presents the results of subgroup analyses.

Meta-regression analysis

Meta-regression was performed to identify statistically significant covariates affecting diagnostic accuracy. The result of the meta-regression analysis for patients with suspected IgG4-SC versus those without was approaching statistical significance for higher specificity (relative specificity = 1.38, $p = 0.05$). This finding may support the efficacy of IgG4 in the differential diagnosis of IgG4-SC. Studies that used retrospective study design may yielded lower sensitivity of serum IgG4 than that of prospective studies (relative sensitivity = 0.9, $p = 0.22$). Articles that assessed patients with elevated serum IgG4 may have demonstrated decreased specificity of serum IgG4 compared to those that did not (relative specificity = 0.08, $p = 0.03$). Table 3 lists the outcomes of meta-regression analyses.

DISCUSSION

The results of this study underscore the enduring relevance of serum IgG4 within the landscape of modern diagnostic frameworks. Currently, the diagnosis relies on the 2020 revised comprehensive diagnostic criteria, which integrate serological findings with imaging and histopathology[6]. This study examined the standard clinical cutoff value of >135 mg/dL and found that it was highly sensitive. This finding supports the continued use of this threshold as an effective initial evaluation tool in clinical practice.

The clinical value of serum IgG4 extends beyond initial detection. Serum IgG4 levels higher than 905 mg/dL have been associated with multi-organ involvement, underscoring their utility in assessing disease severity[34]. Serum IgG4 is an integral component in the monitoring of therapeutic responses. Subsequent to the administration of a standardized treatment protocol, a significant decrease in serum IgG4 levels was observed[34]. In patients suffering from anti-neutrophil cytoplasmic antibody-associated vasculitis, there is a notable elevation in IgG4 levels. However, these levels remain consistent following treatment, indicating their potential to serve as a diagnostic criterion for differentiating this condition from IgG4-RD[34].

A salient finding of our subgroup and meta-regression analyses is the variation in diagnostic performance across different organ manifestations. Specifically, serum IgG4 demonstrates higher diagnostic specificity in patients with suspected IgG4-SC. Subgroup analysis for IgG4-SC revealed a notably high specificity, though this was accompanied by a reduced sensitivity. The meta-regression analysis further corroborated this finding, demonstrating that the specificity for IgG4-SC compared to other manifestations nearly reached statistical significance. This finding indicates that, within the context of biliary strictures, an elevated serum IgG4 level serves as a robust predictor for distinguishing IgG4-RD from mimics. Although one included study employed considerably higher cutoffs—such as 540 mg/dL for bile duct specificity—to enhance confidence, the present data indicates that the biomarker offers significant diagnostic clarity even at standard levels in biliary cases. Conversely, in other manifestations, such as retroperitoneal fibrosis or kidney disease, the diagnostic performance might be more variable, necessitating a more cautious interpretation of serological results due to limited data regarding serum IgG4.

Notwithstanding the considerable sample size of the meta-analysis, there are several limitations to consider. The majority of the included studies employed a retrospective design. Spectrum bias was identified in two studies, particularly those that included only patients with already elevated serum IgG4 levels. The exclusion of seronegative IgG4-RD patients appears to



introduce a bias, potentially skewing the reported sensitivity and specificity values. The histopathology diagnosis was not consistently applied as a reference standard. Obtaining definitive biopsy specimens from deep-seated organs such as the pancreas or retroperitoneum is technically challenging and often yields insufficient tissue for evaluating classic features like storiform fibrosis[7,8]. As our meta-regression suggests, organ-specific differences in accuracy may exist. Hence, future research endeavors might be advised to prioritize the establishment of optimized, organ-specific cut-off values.

CONCLUSIONS

The outcomes of this meta-analysis validated that serum IgG4 serves as an accuracy tool for the initial evaluation of patients with suspected IgG4-RD. Another potential benefit of this biomarker is its specificity to IgG4-SC.

DECLARATIONS

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Comflict of interest

The authors declare that there is no conflict of interest.

CRediT authorship contribution statement：

Cheng-Chieh Chen: Data curation; formal analysis; methodology; writing – original draft; Supervision; Validation; Writing – review & editing. **Chao-Ping Chen:** Conceptualization; Data curation; formal analysis; methodology; writing – original draft. **Hsiu-Ling Lin:** Investigation; Data curation; formal analysis; software; writing – original draft.

Institutional Review Board Statement

This meta-analysis examined effect sizes reported in existing articles, thus satisfying the criteria for exemption from institutional review board review.

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FIGURE LEGENDS

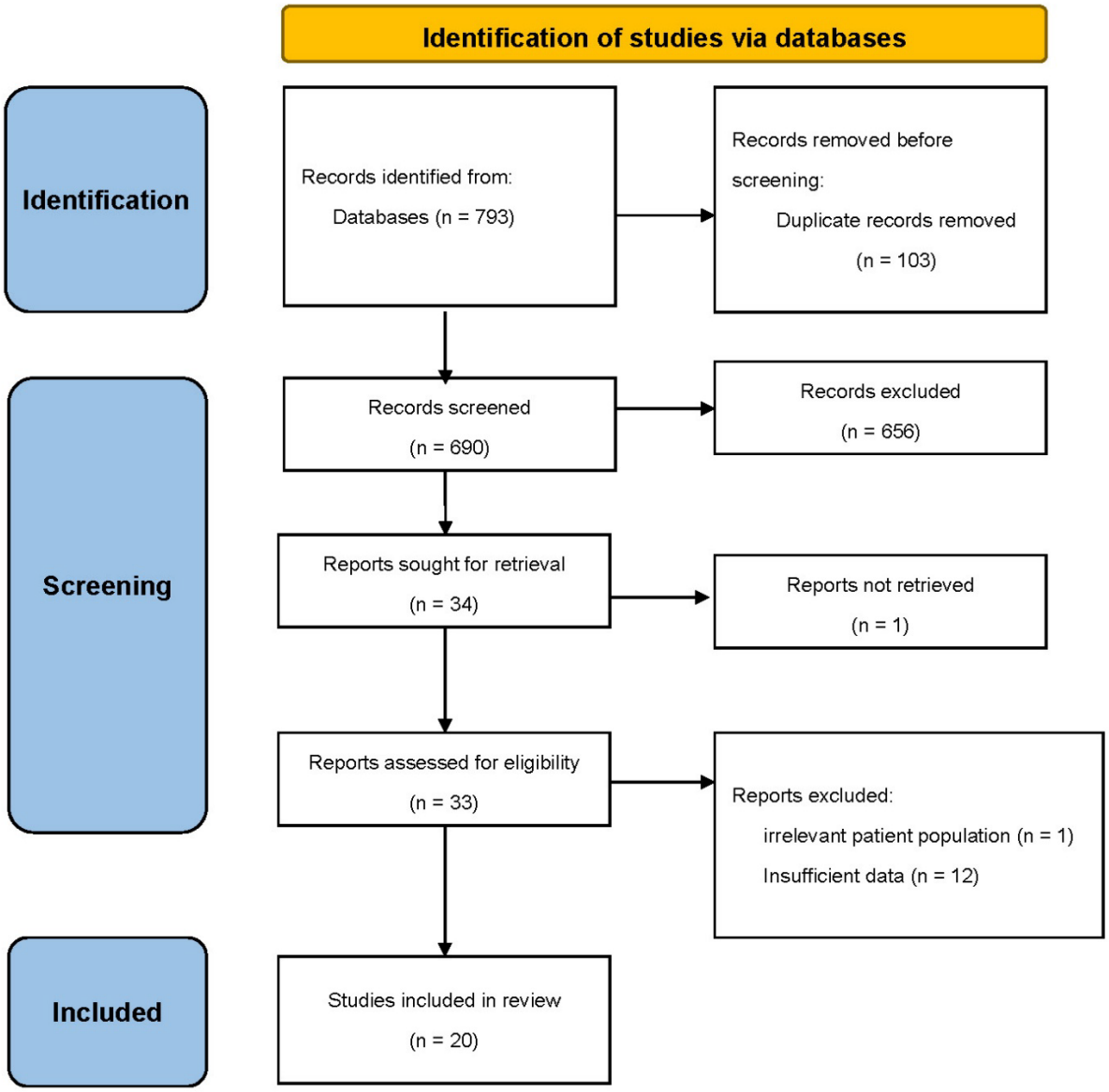


Figure 1. Flow diagram of literature search

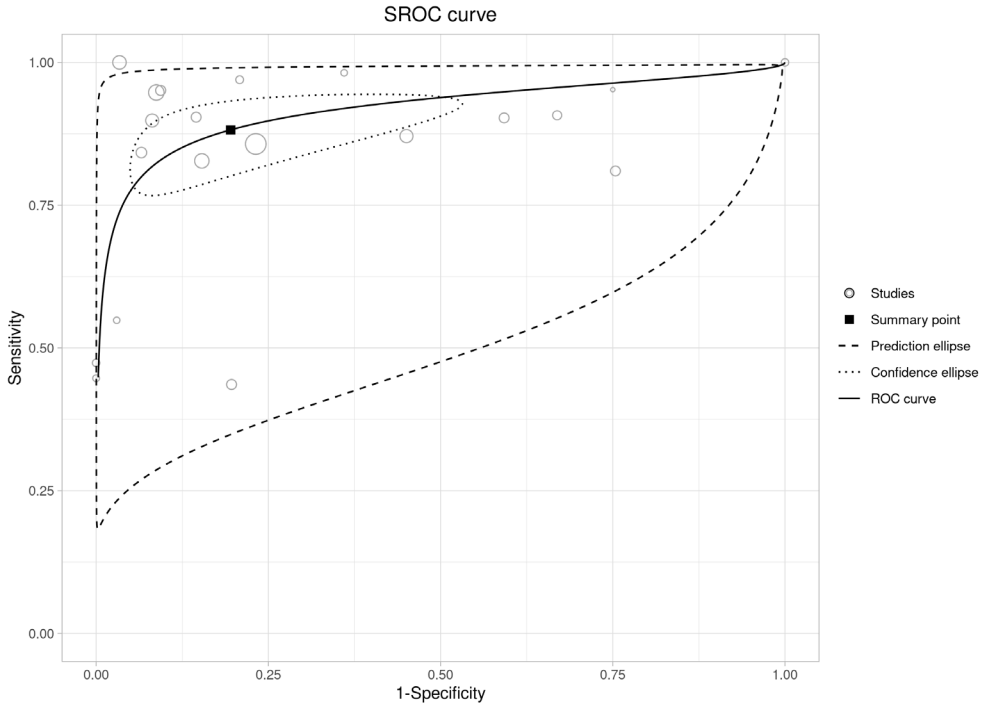


Figure 2. Summary estimate of the SROC curve indicates a pooled sensitivity of 88.2% (95% CI: 80.3% to 93.2%) and a pooled specificity of 80.5% (95% CI: 57% to 92.8%) of serum IgG4. (CI: confidence interval)

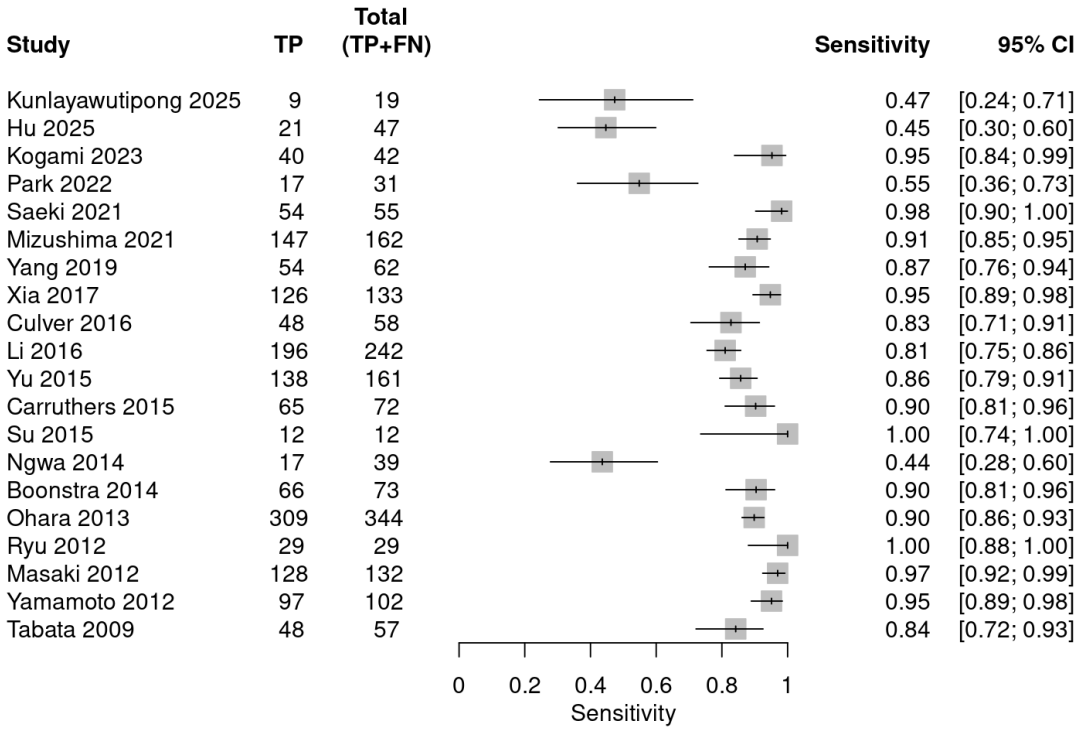




Figure 3. Forest plot showing the sensitivity with 95% CI of serum IgG4 of the included studies. (CI: confidence interval, FN: false negative, TP: true positive)

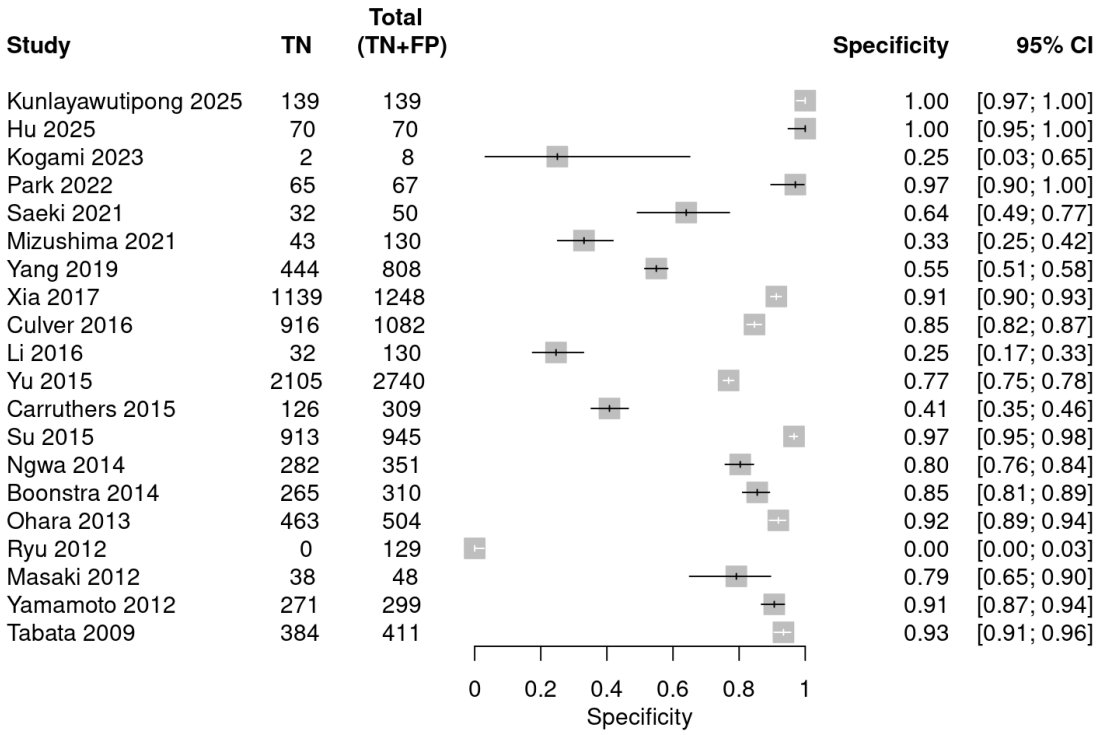


Figure 4. Forest plot showing the specificity with 95% CI of serum IgG4 of the included studies. (CI: confidence interval, FP: false positive, TN: true negative)



Figure 5. Risk of bias in each study.

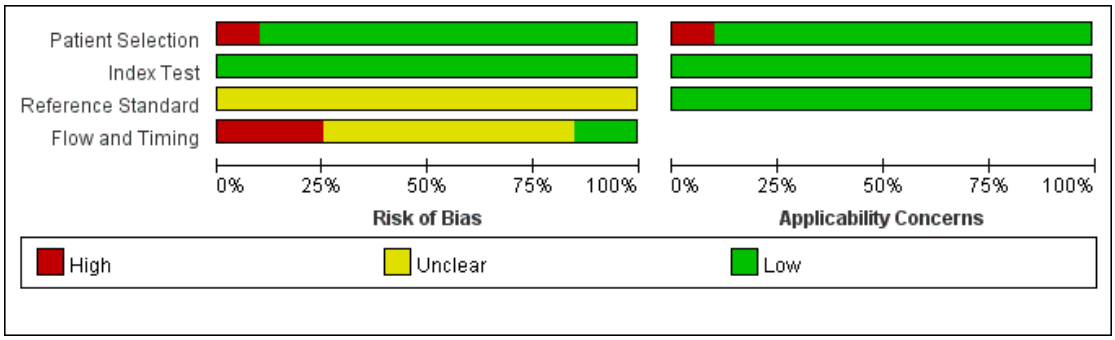


Figure 6. Overall quality of the included studies.



TABLES

Table1. Characteristics of studies

Table 1. Characteristics of studies

Study	Study design	Number of participants (total / data extraction)	Age	Participant population	Index test	Detection technique	IgG4 cut-off value (mL/dL)	Affected organ	Pathological diagnosis
Kunlayawutipong 2025	retrospective	(158/158)	59.3 ± 15.6 (mean, SD)	patients with benign biliary strictures	NA	NA	540	bile duct	IgG4-related cholangitis
IIu 2025	retrospective	(117/117)	60.0 ± 11.4 (mean, SD)	patients with retroperitoneal fibrosis	NA	NA	135	retroperitoneum	IgG4-related retroperitoneal fibrosis
Kogami 2023	retrospective	(50/50)	61 (median)	patients with IgG4-related disease	NA	NA	135	NA	IgG4-related disease
Park 2022	retrospective	(98/98)	65 ± 11.9 (mean, SD)	patients with suspected IgG4-related cholangitis	NA	NA	135	bile duct	IgG4-related cholangitis
Saeki 2021	retrospective	(105/105)	69.9 ± 9.4 (mean, SD)	patients with suspected IgG4-related kidney disease	NA	NA	135	kidney	IgG4-related kidney disease
Mizushima 2021	consecutive, retrospective	(292/292)	67 (median)	patients with IgG4-related disease	NA	NA	135	NA	IgG4-related disease
Yang 2019	retrospective	(870/913)	NA	patients with IgG4-related disease	BN II analyser	immunonephelometry	160	lymph nodes, pancreas, lacrimal glands	IgG4-related disease
Xia 2017	retrospective	(1381/1381)	60 (median)	patients with suspected IgG4-related disease	Siemens BN II	immunonephelometry	201	NA	IgG4-related disease
Culver 2016	consecutive, retrospective	(1510/1140)	59.4, 3-93 (median, range)	patients with suspected IgG4-related disease	Siemens BN II	immunonephelometry	140	NA	IgG4-related disease
Li 2016	retrospective	(372/372)	56.5 ± 13.2 (mean, SD)	patients with suspected IgG4-related disease	Siemens BN prospec-I	immunonephelometry	135	autoimmune pancreatitis, sialadenitis,dacryoadenitis	IgG5-related disease
Yu 2015	retrospective	(2901/2901)	58.4 ± 16.1 (mean, SD)	patients with suspected IgG4-related disease	Siemens BN II	immunonephelometry	135	autoimmune pancreatitis, ophthalmic disease, sialadenitis,lymphadenopathy	IgG4-related disease
Carruthers 2015	retrospective	(381/381)	48 ± 17 (mean, SD)	patients with suspected IgG4-related disease	NA	NA	135	NA	IgG4-related disease
Su 2015	prospective	(957/957)	NA	patients with suspected IgG4-related disease	Siemens BN prospec-I	immunonephelometry	135	NA	IgG4-related disease



Ngwa 2014	retrospective	(390/390)	54.9 ± 18.1 (mean, SD)	patients with elevated serum IgG4	NA	immunonephelometry	240-280	autoimmune pancreatitis, IgG4-related sclerosing cholangitis, IgG4-related retroperitoneal fibrosis	IgG4-related disease
Boonstra 2014	retrospective	(383/383)	65.2 ± 14.1 (mean, SD)	patients with primary sclerosing cholangitis and IgG4-related sclerosing cholangitis	Siemens BN II, Siemens BN prospec-I	immunonephelometry	140	IgG4-related sclerosing cholangitis	IgG4-related sclerosing cholangitis
Ohara 2013	retrospective	(848/848)	65.2 ± 10.2 (mean, SD)	patients with IgG4-related sclerosing cholangitis	NA	NA	135	IgG4-related sclerosing cholangitis	IgG4-related sclerosing cholangitis
Ryu 2012	consecutive, retrospective	(158/158)	51.4 ± 20.3 (mean, SD)	patients with elevated serum IgG4	NA	immunonephelometry	140	pancreas, bile ducts, orbit	IgG4-related disease
Masaki 2012	retrospective	(180/180)	NA	patients with suspected IgG4-related disease	NA	NA	135	lacrimal gland, parotid gland, submandibular gland	IgG4-related disease
Yamamoto 2012	prospective	(401/401)	NA	patients with suspected IgG4-related disease	Behring nephelometer	NA	144	NA	Mikulicz'sdisease, Kuttner's tumor, IgG4-related dacryoadenitis, autoimmune pancreatitis
Tabata 2009	retrospective	(468/468)	NA	patients with suspected pancreatobiliary, allergic, or immunological diseases	NA	immunonephelometry	135	pancreas, salivary gland	autoimmune pancreatitis, Mikulicz's disease

NA: not available; SD: standard deviation

Table2. Subgroup analyses of the diagnostic accuracy of serum IgG4

Table 2 Subgroup analyses of the diagnostic accuracy of serum IgG4

Subgroup	Number of studies	Number of lesions	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Study design				
Prospective	2	1358	96.5 (76.9%-99.6%)	94.4 (36.7%-99.8%)
Retrospective	18	10292	87.1 (78.6%-92.6%)	77.4% (52.1%-91.5%)
Participant population				
Patients with suspected IgG4-related sclerosing cholangitis	4	1487	76.2% (48.3%-91.7%)	97.4% (78%-99.8%)
Patients with elevated serum IgG4	2	548	76.2% (46.3%-97.8%)	7% (2%-75.8%)
Serum IgG4 cut-off value				
135 (mL/dL)	12	6769	87.9% (79.1%-93.4%)	81% (56.9%-93.3%)
Detection technique				
Immunonephelometry	10	9020	87.9 (78%-93.7%)	69.3 (33.4%-91.1%)

CI: confidence interval



Table3. Estimates of metaregression

Table 3 Estimates of metaregression

	Estimate			
covariate	Relative sensitivity (95% CI)	p-value	Relative specificity (95% CI)	*p*-value
retrospective vs prospective	0.9 (0.902-0.904)	0.22	0.82 (0.819-0.822)	0.39
patients with suspected IgG4-related sclerosing cholangitis vs not	0.85 (0.63-1.14)	0.14	1.38 (0.98-1.93)	0.05
patients with elevated serum IgG4 vs not	0.98 (0.74-1.3)	0.88	0.08 (0.003-2.63)	0.03

CI: confidence interval



Diagnostic accuracy of serum IgG4 for IgG4-related disease: A meta-analysis

血清 IgG4 偵測 IgG4 相關疾病的準確度：統合分析

陳兆平[1]　林秀玲[2]　陳正杰[3*]

中文摘要

背景：IgG4 相關疾病（IgG4-RD）是一種全身性、免疫系統引起的纖維炎症性疾病，可能影響多重器官系統。IgG4-RD 的臨床表現通常不具特異性，可能與惡性腫瘤的表現相似。誤診可能導致不必要的手術。血清 IgG4 是該疾病的血清生物標記。然而，血清 IgG4 的診斷應用仍有擴展的空間。本研究的目的是重新評估血清 IgG4 在檢測 IgG4-RD 方面的效能。**方法：**透過 PubMed、Embase 及 Cochrane 文獻庫進行文獻檢索，以篩選符合資格的論文。納入研究須包含疑似或確診的 IgG4-RD 患者，採用組織病理診斷作為黃金標準進行確認。此外，納入的文獻須提供足夠數據以進行統合分析。本統合分析採用 bivariate random-effects model。**結果：**本研究共納入 20 篇論文，涵蓋 11,650 名患者。統合分析顯示，血清 IgG4 在診斷 IgG4-RD 方面的敏感度為 88.2%，特異度為 80.5%。針對疑似 IgG4 相關硬化性膽管炎（IgG4-SC）患者的分析顯示，其敏感度為 76.2%，特異度為 97.4%。以 135 mg/dL 作為閾值，敏感度為 87.9%。**結論：**本研究指出，血清 IgG4 可作為疑似 IgG4 相關疾病患者初期評估的工具。IgG4 的另一項潛在優勢在於其對 IgG4 相關硬化性膽管炎的高特異性。

關鍵字：IgG4 相關疾病、血清 IgG4、統合分析、敏感度、特異度

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Original Research Article

Test-Retest Reliability and Ceiling Effect of Shih-Wu EADL Evaluation Tool (SWEET) for People with Schizophrenia

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ABSTRACT

Background and purpose: Due to changes in technology, many activities of daily living have become electronic, the "Shih-Wu EADL Evaluation Tool" (SWEET) is an electronic activities of daily living (EADL) assessment tool developed by occupational therapists. The purpose of this study was to explored a further reliability and validity analysis of the SWEET, including test- retest reliability and ceiling effect. ***Methods:*** The participants were 22 healthy people, and 50 people with schizophrenia aged 20–64 were recruited in this study on a voluntary basis. The 72 individuals were each asked to answer the SWEET test twice, with a one-week interval between the two tests. ***Results:*** The ICC of the two tests was 0.987 in healthy people, and the ICC of the two tests was 0.961 in people with schizophrenia, which is high reliability standards. And no ceiling effect appeared. ***Conclusion:*** Our preliminary findings show that the SWEET has high test-retest reliability for people with schizophrenia, supporting the future application of SWEET as an assessment tool for electronic activities of daily living (EADL).

Keywords: Clinical assessment, occupational therapy, Activities of Daily Living

INTRODUCTION

Our society and daily life are being impacted by artificial intelligence (AI), and an individual's ability to use electronic tools may affect their daily performance. In the past few years, scholars have mainly divided activities of daily living into two categories, including basic activities of daily living (BADL) and instrumental activities of daily living (IADL). Basic activities of daily living include personal hygiene, eating ability, and mobility, putting on



and taking off clothing and footwear, urinary and bowel control, etc.; instrumental activities of daily living include shopping, money management, using public transportation, using the phone, medication compliance and crisis management[1]. With the advancement of the times, the forms of many activities of daily living have changed in the past. Due to changes in technology, many activities of daily living have become electronic, which is a trend that cannot be ignored in the future[2]. For many people with or without schizophrenia, many daily life activities that they were familiar with in the past may now or in the future need to be performed electronically/informatizationally. These activities include managing health, managing money, shopping, and entertainment and social activities, and the aforementioned electronic activities were oriented across past BADLs and IADLs[3]. However, many people with schizophrenia are not familiar with the operation of electronic products or interfaces.

As more and more activities of daily living may be done electronically by elderly people. Therefore, occupational therapists in Taiwan have proposed the concept of so-called "electronic activities of daily living (EADL)" in addition to the existing BADL and IADL, and initially published the "Shih-Wu EADL Evaluation Tool"[3], it is expected that this study can verify the reliability and validity of this new assessment tool to further promote the concept of EADL. The concept of "electronic activities of daily living (EADL)" may include the following: “Electronic money management”**,** such as electronic money refers to currency that exists in bank computer systems and can be used to facilitate electronic transactions, online transfers and online tax refunds; “Information social activities” , such as online gatherings and online meetings; “Online shopping” such as electronic shopping, including online payments, online credit cards, electronic orders in electronic stores and online bookstores; “Online or electronic entertainment activities” including watching movies online, listening to music online, reading e-books or online news, etc[3].

The above-mentioned daily life activities could be carried out in a "non- electronic management" way in the past, but it may be necessary to adopt "electronic management" now or in the future[3]. Whether future patients or the elderly can have good "electronic activities of daily living" (EADL) will determine whether they can adapt to the future world.

The current functional tests of daily living in occupational therapy, including the Chu's ADL Test, the Pap Scale, etc., do not focus on "electronic activities of daily living" (EADL), but more and more aspects of daily living are included. Activities will be conducted in an information-based manner in the future. Many current daily life function tests may no longer be able to reflect future information-based daily life activities. Therefore, it is important and urgent to develop a new "EADL Evaluation Tool" and conduct basic reliability and validity verification. Currently, the "Shih-Wu EADL Evaluation Tool (SWEET)" has been developed but has not yet undergone sufficient reliability and validity verification[3].

Among them, test-retest reliability are important indicators of whether a new assessment tool can be used in clinical occupational therapy. If there is insufficient test-retest reliability, its clinical practicability will be questioned[4-7]; and the ceiling effect is also an indicator to examine the blind spots of a new assessment tool. The definition of ceiling effect refers to whether the evolution tool is too easy for certain groups and does not discriminate enough, resulting in the scores of the test subjects are concentrated in the very high scores, which means that it is impossible to distinguish the ability differences between some high scorers. The criterion is generally based on whether the proportion of subjects who obtain the highest score in the assessment tool reaches 20%[8]. Criterion-related validity should also be an important issue in the development of a new assessment tool, criterion-related validity is important because it can correlate test scores with concrete, objective real-world performance, thereby ensuring that the test has actual predictive power or judgmental value. It can effectively predict the future behavioral performance of test takers, such as using aptitude test scores to predict college academic performance or using aptitude tests to predict job performance. It can show whether test scores are related to existing standards and confirm whether the test can replace expensive or complex testing methods. Compared to theoretical validity, criterion-related validity verifies whether the test truly measures what it intends to measure through actual statistical data[4, 6]. However, because "electronic activities of daily living" (EADL) is a relatively new concept, and no occupational therapy assessment tools have previously been used to assess EADL, this study only explores test-retest reliability.

The purpose of this study is to conduct a further reliability and validity analysis of the "Shih-Wu EADL Evaluation Tool"[3], including

test- retest reliability and ceiling effect. And further compare the differences in the performance of "electronic activities of daily living" (EADL) between generally healthy people and the people with schizophrenia. The purpose of this study is as follows:

1. Construction of test-retest reliability of "Shih-Wu EADL Evaluation Tool (SWEET)" in healthy people.
2. Construction of test-retest reliability of "Shih-Wu EADL Evaluation Tool (SWEET)" for the people with schizophrenia.
3. Ceiling effect of "Shih-Wu EADL Evaluation Tool (SWEET)" in healthy people.
4. Ceiling effect of "Shih-Wu EADL Evaluation Tool (SWEET)" on the people with schizophrenia.

MATERIALS AND METHODS

This study examined the test-retest reliability and ceiling effect of the "Shih-Wu EADL Evaluation Tool (SWEET)".

Participants

This research recruited participants in New Taipei City. A total of 22 healthy people aged between 20 and 64 years old, and 50 people with schizophrenia aged between 20 and 64 years old, excluding those with visual impairment, collect the test is being carried out. Ethical approval for the study was granted by the Institutional Review Board (IRB).

Procedure

Step 1: Continuously test the "Shih-Wu EADL Evaluation Tool" (SWEET) on 22 healthy people aged between 20 and 64 years old, and 50 people with schizophrenia aged between 20 and 64 years old.
Step 2: One week later, conduct the second test of "Shih-Wu EADL Evaluation Tool" (SWEET).
Step 3: Use SPSS software to conduct test-retest reliability analysis and Ceiling Effect.
Step 4: Compare the differences in "electronic activities of daily living (EADL)" between healthy people and the elderly.

Measures

Shih-Wu EADL Evaluation Tool (SWEET): 25 questions in total, targeting "electronic money management", "information social activities", "online shopping", "online or electronic entertainment activities", etc. in daily life activities Designed for. The highest score is 50 points and the lowest score is 1 point[3].

Data Analysis

All statistics were conducted using SPSS20.0 (SPSS Japan, Tokyo, Japan) with $p<0.05$ considered to be statistically significant. First, the intra-class correlation coefficient (ICC) was used to estimate the test-retest reliability by comparing the test scores from the two SWEET (test-retest reliability). An ICC value ≥ 0.80 indicates high reliability, 0.60-0.79 indicates moderate reliability, and < 0.59 indicates poor reliability [9]. And the t-test was used to compare the different between healthy people aged 20 to 64 years old, and 50 healthy elderly people aged 65 to 85 years old.

The test-retest reliability of SWEET was verified using the intraclass correlation coefficient (ICC), and a two-way random model was used to calculate the ICC and 95% confidence interval[10, 11]. The ICC can compare the proportion of repeated measures results relative to individual differences, thus representing the stability of scores over repeated measures[11]. Compared to the Pearson correlation coefficient, which only reflects linear association, the ICC also considers agreement and is more sensitive to systematic biases that may occur between repeated measures. This study will use an ICC ≥ 0.70 to represent acceptable reliability and ≥ 0.90 to represent excellent test-retest reliability[12].

The standard error of measurement (SEM) was used to verify random measurement error[13]. The SEM is estimated through the ICC and conceptually represents the fluctuation of repeated measures scores due to random error, assuming the subject's ability remains constant [13]. SEM is further converted into the minimum detectable change (MDC95) as a threshold for determining "true changes beyond measurement error" at a 95% confidence level, thereby improving the interpretability of the score [14]. To facilitate comparisons between different scales or samples, this study converts the calculated MDC95 into a relative index, MDC95, expressed as the ratio of MDC95 to the maximum possible score. An MDC95% below 10% of the maximum possible score is considered excellent, while 10%–30% is considered acceptable. The calculation formulas for SEM and MDC95 are as follows[15]:

$$SEM = SD_{baseline} \times \sqrt{1 - ICC}$$
$$MDC_{95} = 1.96 \times \sqrt{2} \times SEM$$

Ethical considerations

Ethical approval was given by the medical ethics committee of Fu Jen Catholic University Institutional Review Board (IRB) on 2024 with the following reference number: C112082. All survey and audit data were collected anonymously. Written consent was taken immediately

prior to the test and participants were reminded that this could be withdrawn at any time, and not having a financial interest with researchers.

RESULTS

Test-retest reliability of the SWEET in healthy people aged between 20 and 64 years old (n=22)

For healthy subjects aged between 20 and 64 years old, the average score for the first test was 42.182, and the average score for the second test was 42.500. The intraclass correlation coefficient (ICC) was determined to compare the test scores from the two SWEET. The ICC of the two tests was 0.987, Regarding the measurement error, the SEM score for the healthy adult group was 0.5 and the MDC95 score was 1.5 (approximately 3.0% of the maximum possible score), as shown in Table 1.

Test-retest reliability of the SWEET in people with schizophrenia aged between 20 and 64 years old (n=50)

For subjects with schizophrenia between 20 and 64 years old, the average number for the first test was 16.9, and the average number for the second test was 18.1. The intraclass correlation coefficient (ICC) was determined to compare the test scores from the two SWEET. The ICC of the two tests was 0.961, Regarding the measurement error, the SEM score for the schizophrenia group was 2.5 and the MDC95 score was 6.9 (approximately 13.8% of the maximum possible score), as shown in Table 1.

3. Ceiling Effect, and the difference in scores between 22 healthy people aged 20 to 64 years old and 50 people with schizophrenia aged 20 to 64 years old.

In this study, none of them had perfect scores, and no Ceiling Effect appeared. However, the scores of the two groups were very different, as shown in Table 1 and Table 2.

DISCUSSION

ADL is an important function for people with schizophrenia. Validate and develop new evolution tools of ADLs are worthy issue for occupational therapists [1]. However, with the evolution of the times, many ADL activities are no longer performed in the way that people were familiar with in the past, but in an " electronic management " way. Carry out, including ordering food, medical treatment, payment, etc. Therefore, in addition to basic activities of daily living (BADL) and instrumental activities of daily living (IADL), the concept of so-called "electronic activities of daily living" (EADL) will become more important. EADL is not a project independent of BADL and IADL, but refers to the fact that many past BADL and IADL projects will need to be carried out in an "electronic management" manner in the future. "Shih-Wu EADL Evaluation Tool" (SWEET) is an evaluation tool developed specifically for EADL.

Test-retest reliability is important because it measures the consistency and stability of results obtained by a measurement tool when measuring the same subject at different points in time[5]. Simply put, it confirms whether the measurement results are reliable and will not fluctuate significantly due to time variations. It reflects the changes in a subject's scores between two tests and is an important indicator of test stability. High test-retest reliability indicates that the measurement tool effectively controls for random errors caused by time differences, ensuring that the measured attributes are consistent[5,16]. From a clinical occupational therapy assessment perspective, high reliability is the foundation for tool acceptance. If a daily living skills test yields a high result today but a low result tomorrow, the test is not valuable. The level of test-retest reliability directly determines whether the measurement results are trustworthy. Without test-retest reliability, researchers cannot determine whether the difference in measurement results is due to changes in the subject's actual abilities or errors in the measurement tool itself[5,16]. This study found that SWEET has high test-retest reliability for both general healthy people and people with schizophrenia, which are 0.987 and 0.961 respectively, both reaching above 0.8, which is high reliability standards, as shown in Table 1.[9]. In this study, it was also found that there was no ceiling effect in SWEET, which shows that the SWEET score are clinically distinguishable. Regarding random measurement error, the 95% SEM and MDC were lower in the healthy adult group (approximately 3.0%), while they were higher in the schizophrenia group (approximately 13.0%). This indicates that the measurement may more accurate in healthy adults, while scores in the schizophrenia group may be affected by state fluctuations or non-systematic factors. However, the 95% MDC for both groups was below 30%, remaining within an acceptable range overall. This result suggests that the impact of random measurement error on both groups is limited, and score fluctuations are not primarily driven by measurement error. When a participant's score change exceeds the corresponding 95% MDC, the likelihood of this change being

caused by measurement error is limited, and it can be reasonably interpreted as a change in the participant's true ability, further improving the interpretability of the score-based method.

The "ceiling effect" is very important in statistics, psychological testing and medical pharmacology, mainly because it limits the discriminative power of measurement tools, making it impossible to accurately assess the differences among high-performing individuals or the maximum effect of intervention. When the test questions are too easy, most test takers' scores are concentrated around the full score, forming a "ceiling" that makes it impossible to distinguish the real ability difference between top performers and those of average or above-average ability. In other words, the maximum score set by the measurement tool limits the performance of high-performing individuals, causing the data to be overly concentrated in the upper limit area, making it impossible to accurately measure the actual differences between high-performing individuals[4]. In this study, the "Shih-Wu EADL Evaluation Tool" (SWEET) did not produce a ceiling effect, showing that SWEET can distinguish the real ability difference between top performers and those of average or above-average ability, and more accurately reflect the effectiveness of the scores, as shown in Table 2.

In terms of scores, this study also found that the scores of healthy people were much higher than those of people with schizophrenia between the ages of 20 and 64, and the difference reached a statistically significant value. The ability to carry out electronic daily life activities may obviously weak for people with schizophrenia, including ordering food, seeking medical treatment, paying bills, etc. Combining the above two phenomena, if the electronic activities of the people with schizophrenia are daily Living (EADL) cannot be effectively improved, which may be an important factor that will prevent the people with schizophrenia from living independently in the future. Exploring the reliability and validity of new occupational therapy assessment tools is a very meaningful clinical research topic[16,17], so we believe that the findings of this study are worthy of reference by future clinical occupational therapists and researchers.

The future is ushering in an artificial intelligence (AI) era, where familiar daily activities will become increasingly digitized. AI will even reshape daily life patterns, allowing users to manage their homes through voice control or automated scheduling. Applications will utilize real-time traffic data to automatically calculate the fastest routes and predict arrival times. AI translation tools will make cross-language communication more immediate and accurate, breaking down language barriers. Generative AI can assist in writing emails, drawing, or composing music, lowering the creative threshold. All these changes will make the assessment of "electronic activities of daily living" (EADL) even more important. Adapting to such changes is challenging not only for healthy individuals but also potentially impacts the adaptation of mentally ill patients. The "Shih-Wu EADL Evaluation Tool" (SWEET) assesses an individual's ability to use AI or electronic products for daily activities in the current situation. However, as AI evolves rapidly in the future, the "Shih-Wu EADL Evaluation Tool" (SWEET) may need to be updated to a second, third, and subsequent versions to accommodate the evolving impact of AI on daily life.

This research project still has its limitations, as detailed below. Only 22 healthy people aged between 20 and 24 years old and 50 people with schizophrenia aged between 20 and 24 years old took the tests. Future work will adopt other test tool scores for comparison. This research is based on convenience sampling, so its findings may not be generalized to population. In addition, inter-rater reliability (IRR) is also an indicator of the credibility of a new assessment tool because it ensures the consistency, objectivity, and accuracy of measurement results, avoiding errors caused by individual rater factors. When a study involves multiple observers or coders, IRR measures whether different raters agree on the same set of data. In summary, inter-rater reliability is the core procedure for converting subjective observations into objective data, and it is indispensable for ensuring the "reliability" of a measurement tool among different users. Future research could also validate the inter-rater reliability of the "Shih-Wu EADL Evaluation Tool" (SWEET) to explore whether SWEET might be subject to errors due to individual rater factors, thus making this new assessment tool more clinically applicable. This study tested 22 healthy individuals and 50 individuals with schizophrenia, but did not analyze factors such as age, education, background, or occupation to explore which factors might influence performance on "electronic activities of daily living" (EADL). In the future, factor analysis could be conducted on individuals' age, education, background, occupation, and their scores on the "Shih-Wu EADL Evaluation Tool" (SWEET). In the future, the method of



extreme groups in item analysis can also be used in statistics. The resulting data could serve as an important reference for future clinical practice. The newly developed assessment tool "Shih-Wu EADL Evaluation Tool" (SWEET) is currently conducted as a paper-and-pencil test. In the future, we may also consider using computers or mobile phones as testing platforms to increase the convenience of the test.

CONCLUSIONS

Whether a medical profession can adapt to changing times and develop new clinical assessment tools is crucial to its continued progress. The “Shih-Wu EADL Evaluation Tool” (SWEET) is a novel ADL assessment tool developed in recent years by occupational therapists in Taiwan. This investigation draws the following conclusions and suggestions:

1. "electronic activities of daily living" (EADL) is a topic worthy of discussion by occupational therapists. Given that many daily living activities will be digitized in the future, more assessment tools should be available to assessment the electronic activities of daily living level of people with schizophrenia.
2. Shih-Wu EADL Evaluation Tool (SWEET) has high test-retest reliability for people with and without schizophrenia aged 20 to 64 years old.
3. In order to enhance the credibility of the reliability-validity analysis, the SWEET test uses a much larger sample size and is compared with other attention tests for reliability and validity.
4. The criterion-related validity and test-retest reliability of SWEET should be studied for different types of diagnosis, group and age in the future.

DECLARATIONS

Ethics Approval：

Ethical approval was given by the medical ethics committee of Fu Jen Catholic University Institutional Review Board (IRB) on 2024 with the following reference number: C112082

Conflicting interest and data availability statements：

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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TABLES

Table1. Parameters of test-retest reliability of the SWEET in healthy people and people with schizophrenia

Group	N	Mean (SD) T0	Mean (SD) T1	ICC (95% CI)	SEM	MDC	MDC%	Pear-son_r	p_value
people with schizo-phrenia	50	16.9 (11.7)	18.1 (12.3)	0.96 (0.93 – 0.98)	2.5	6.9	39.3	0.96	< 0.001
healthy people	22	42.2 (4.4)	42.5 (4.4)	0.99 (0.96 – 0.99)	0.5	1.5	3.6	0.99	< 0.001

ICC = intraclass correlation coefficient, two-way random-effects model with absolute agreement, ICC

SEM = standard error of measurement

MDC = minimal detectable change

MDC% = MDC / Mean × 100%

Table2. Parameters of maximum and minimum values of the SWEET in healthy people and people with schizophrenia

		Baseline Mean (SD)	Re-assessment Mean (SD)
healthy peo-ple (n=22)	Max	48	48
	min	36	36
people with schizophrenia (n=50)	Max	45	48
	min	1	1



Test-Retest Reliability and Ceiling Effect of Shih-Wu EADL Evaluation Tool (SWEET) for People with Schizophrenia

施吳氏資訊化日常生活功能評量表應用於思覺失調症患者之再測信度與天花板效應探討

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中文摘要

背景與目的：隨著科技的進步，許多日常生活活動已逐漸電子化。「施吳氏資訊化日常生活功能評量表」是由職能治療師所研發之電子化日常生活活動功能（EADL）評估工具。本研究旨在進一步分析「施吳氏資訊化日常生活功能評量表」（SWEET）的信效度驗證，包括再測信度和天花板效應。**方法：**本研究招募了 22 名健康人和 50 名年齡在 20 至 64 歲之間的思覺失調症患者。分別讓上述 72 位個案作答兩次「施吳氏資訊化日常生活功能評量表」，兩次測驗間隔一週。**結果：**健康族群的兩次測試組內相關係數為 0.987，思覺失調症患者的兩次測試組內相關係數為 0.961，均達高度水平，且未出現天花板效應。**結論：**我們的初步研究結果顯示，「施吳氏資訊化日常生活功能評量表」對精神分裂症患者俱有較高的重測信度，支持未來將「施吳氏資訊化日常生活功能評量表」應用於資訊化日常生活功能之臨床評估。

關鍵字：臨床評估、職能治療、日常生活活動

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Brief Report

Effect of Norepinephrine Dosage on Gastrointestinal Bleeding Diagnosis

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ABSTRACT

This study examined whether reducing the infusion dosage of norepinephrine during angiography of patients with gastrointestinal (GI) bleeding reduces the rate of false negative results. The study cohort comprised 34 patients (male: 19, female: 15, mean age of 64.8 years) with GI bleeding who underwent angiography at a medical center in Taiwan between January 2018 and December 2022. The mean initial blood pressure was 77/58 mmHg, and the average heart rate was 121 beats per minute. All patients received blood transfusion and norepinephrine infusion (mean dose: 3.8 mcg/min) maintain a mean blood pressure of 123/87 mmHg.

Angiography was arranged on an emergency basis. Among these patients, 24 exhibited clear evidence of GI bleeding and subsequently underwent embolization. In the remaining 10 patients, no bleeding was identified during the initial angiography. The norepinephrine infusion dosage of the patients during angiography was reduced about 1.0-1.5 mcg/min until their mean blood pressure was maintained at 91/61 mmHg. Repeat angiography revealed bleeding sites in three patients, who subsequently underwent successful embolization. These findings suggest that in patients receiving norepinephrine infusion for GI bleeding, repeat angiography after a controlled reduction in norepinephrine dosage may reduce the rate of false negative results.

Keywords: angiography, gastrointestinal bleeding, norepinephrine

INTRODUCTION

Gastrointestinal bleeding is a common clinical emergency in internal medicine[1-5]. Most cases originate from the upper gastrointestinal tract or the colon[1-6]; bleeding from the small



intestine accounts for only approximately 5% of cases[7]. The majority of bleeding sources can be identified through endoscopic evaluation; radionuclide-labeled red blood cell scans, computed tomography, and angiography may also be employed. Massive gastrointestinal bleeding often requires treatment through blood transfusion, fluid resuscitation, and the administration of vasopressors[8-13]. Norepinephrine is a commonly used norepinephrine-based vasopressor in clinical settings for patients in shock. However, because norepinephrine induces vasoconstriction in both peripheral and gastrointestinal vessels, it may lead to false negative results during angiography. Accordingly, when angiography fails to detect active bleeding in patients receiving norepinephrine, the general treatment is to gradually reduce the dosage and repeat the angiographic examination to determine whether bleeding has occurred.

A retrospective review was conducted over a 5-year period (2018.1–2022.12) that identified 34 patients with severe gastrointestinal bleeding. The study cohort comprised 19 men and 15 women ranging in age from 48 to 85 years (mean: 64.8 years). Of these patients, 28 were undergoing hemodialysis. The factors that have led to an increasing incidence of GI bleeding in hemodialysis are not clear. The possible bleeding causes was anticoagulation therapy, poor function of platelet and sclerosis of small vessels. All patients were eventually admitted to the intensive care unit. The average volume of hematochezia was 1,455 ccs per day, and the mean number of packed red blood cells transfused per patient was 15 units. The average pretreatment blood pressure was 77/58 mmHg, and the mean heart rate was 121 beats per minute. Because of the patients' hemodynamic instability, norepinephrine (mean dose: 3.8 mcg/min) was administered in addition to the blood transfusions to maintain blood pressure and facilitate diagnostic evaluations.

Panendoscopy revealed gastric ulcers with intragastric blood clots in 8 patients and duodenal ulcers with clots in 21 patients. In the remaining five patients, both panendoscopy and colonoscopy failed to identify a bleeding source. All 34 patients underwent angiographic evaluation (RH modified catheer and Progreat microcatheter, Terumo, Tokyo, Japan). Of these, 2 were diagnosed with gastric bleeding, 17 with duodenal bleeding, 3 with small bowel bleeding, and 2 with ascending colon bleeding. All patients with identified bleeding sites underwent arterial embolization using fiberred platinum microcoils (Boston Scientific, Massachusetts, USA) and spongostan film (Ferrosan, Sydmarken, Soborg, Denmark), achieved hemodynamic stability, and were discharged after a mean hospital stay of 13.5 days. Follow-ups over a period ranging from 1 year and 8 months to 4 years and 7 months revealed no recurrence of gastrointestinal bleeding. In the remaining 10 patients, initial angiography revealed no evidence of active bleeding apart from notable vasoconstriction. These patients had intraprocedure systolic blood pressures exceeding 100 mmHg. The norepinephrine dosage of these patients was gradually reduced about 1.0-1.5 mcg/min (one-quarter to one-third dose) until each patient's systolic pressure had decreased by approximately 20 mmHg (about 3-5 minutes after reduced the norepinephrine dose), at which point angiography was repeated. Active duodenal bleeding was identified in three of these patients, who subsequently underwent successful arterial embolization. These patients were discharged after an average hospital stay of 14 days, and follow-ups ranging from 1 year and 3 months to 2 years and 3 months revealed no recurrence of bleeding.

In patients with severe gastrointestinal bleeding and hemodynamic compromise, angiography is often conducted directly to stop bleeding[1-13]. The benefits of angiography include precise localization of bleeding and the ability to perform immediate postevaluative embolization. Angiography is thus rapid, accessible, and accurate. However, many patients in shock require the administration of norepinephrine, which may induce gastrointestinal vasoconstriction, complicating the angiographic procedure and increasing the risk of false negative results. Historically, patients with negative angiographic findings often underwent exploratory laparotomy, a procedure associated with a high risk of complications, prolonged hospitalization, and increased mortality.

Norepinephrine is a vasoconstrictor commonly used in patients experiencing shock. When combined with appropriate fluid resuscitation and blood transfusion, this medication promotes peripheral vasoconstriction and increases blood pressure. The typical dosage ranges from 2 to 4 mcg/min. Norepinephrine also induces gastrointestinal vasoconstriction, which may hinder the detection of bleeding during angiography by masking active extravasation. However, discontinuing norepinephrine before angiography may induce hypotension. To address this concern, in patients whose initial angiography reveals no evidence of acute bleeding and who have a systolic blood pressure greater than 100 mmHg, norepinephrine dosage can be slightly reduced on site in the angiography suite. Angiography



can be repeated once systolic pressure has decreased by approximately 20 mmHg to reduce the likelihood of false negative results.

In this study, angiography revealed active bleeding or vascular abnormalities in 24 patients, all of whom underwent embolization and subsequently achieved favorable recovery. In the remaining 10 patients, initial angiography revealed no evidence of acute bleeding aside from pronounced vasoconstriction. Of these, three patients were revealed to have active bleeding upon repeat angiography after the dosage of norepinephrine was reduced; all underwent embolization. Notably, each of these three patients experienced an increase in systolic blood pressure exceeding 30 mmHg after embolization. In general, the mortality rate for severe gastrointestinal bleeding ranges from 5% to 30%, rendering prompt treatment essential. To facilitate such treatment, in patients with a systolic blood pressure greater than 100 mmHg in whom no bleeding has been identified on initial angiography, a modest reduction in norepinephrine dosage followed by repeat angiography may reduce the likelihood of false negative results. This approach may prevent unnecessary surgical intervention, improving patient outcomes, reducing health-care costs, and enhancing the overall effectiveness of treatment. However, because the source of gastrointestinal bleeding may be arterial, venous, or mucosal, and because angiography is primarily used to detect arterial bleeding, it is not effective in patients with nonarterial sources of hemorrhage. Selecting patients with a systolic blood pressure greater than 100 mmHg for norepinephrine dose reduction and using a 20 mmHg decrease in systolic pressure as the threshold for repeat angiography thus represents a useful preliminary screening strategy. More cases should be examined to determine and validate the optimal selection criteria.

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FIGURE LEGEND

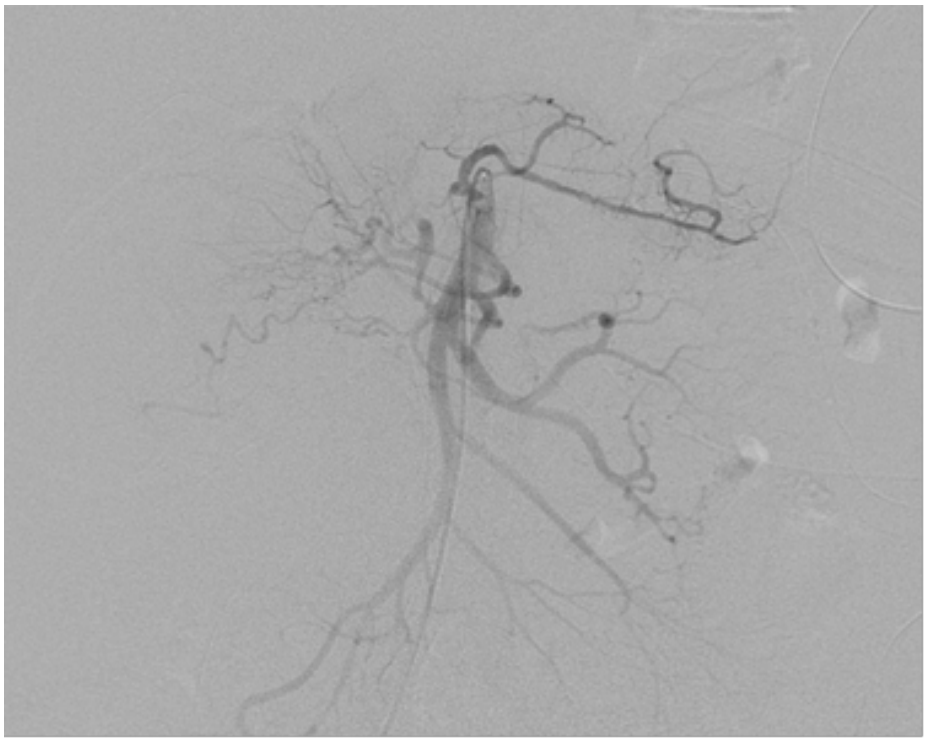


Figure 1 a. 64-year-old man who present gastrointestinal bleeding with norepinephrine infusion treatment. The angiography can not find the bleeder.

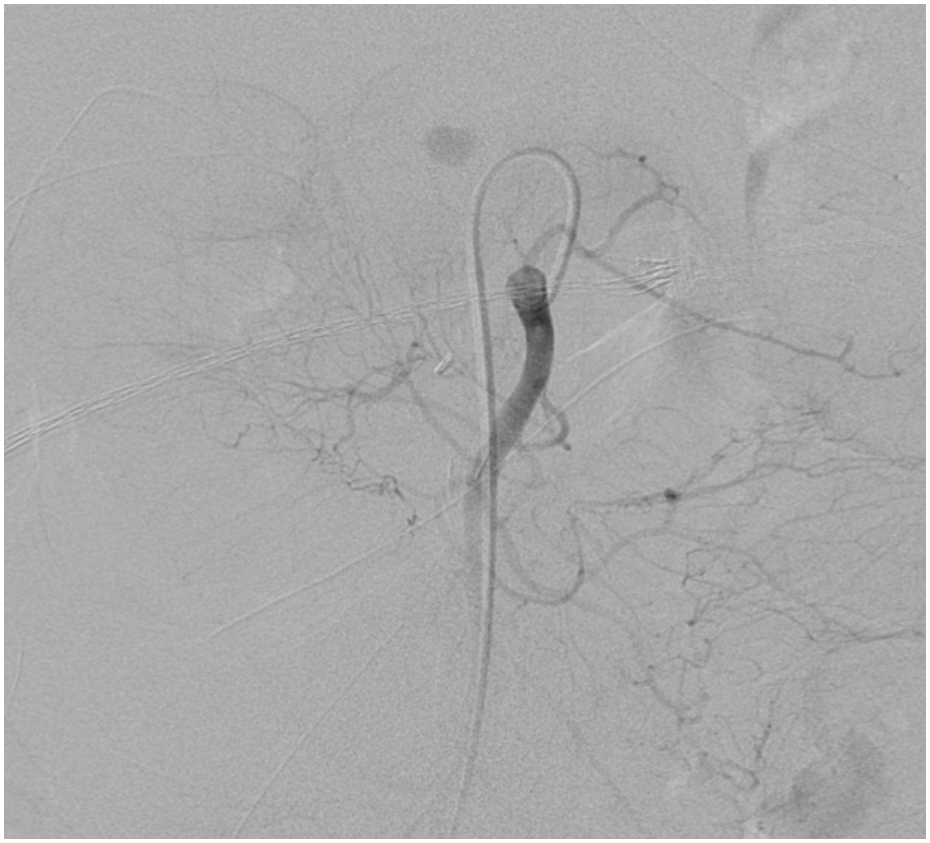


Figure 1b. Repeat angiography after reduce infusion rate of norepinephrine, a bleeder is noted at duodenum (arrow).

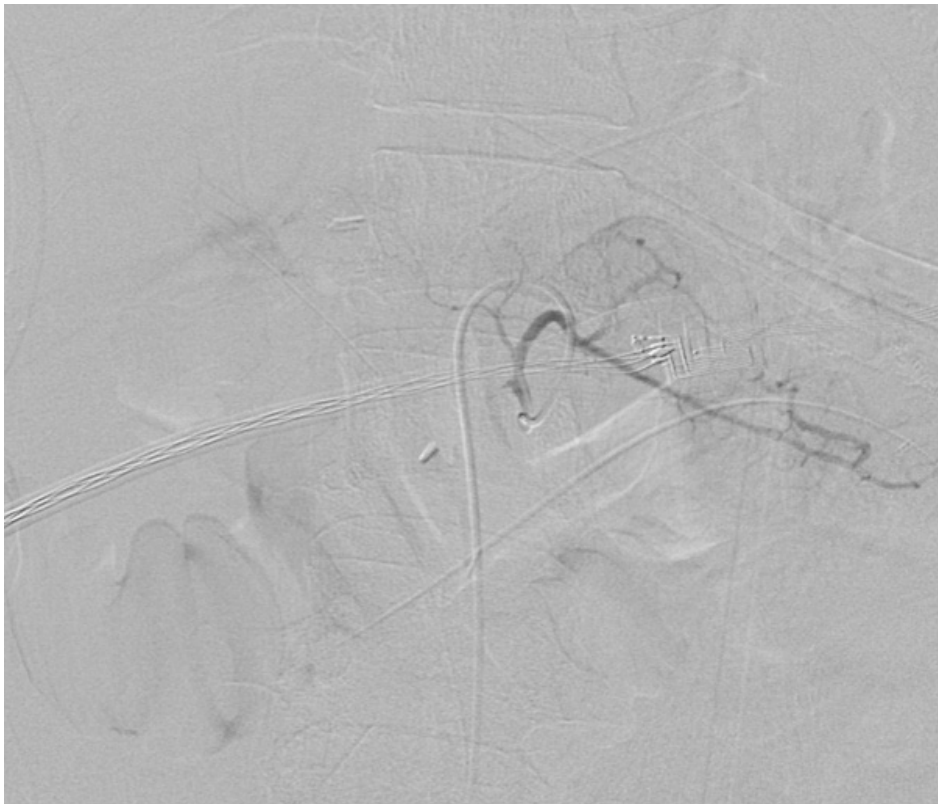


Figure 1c. Repeat angiography after embolization of the bleeder.



Effect of Norepinephrine Dosage on Gastrointestinal Bleeding Diagnosis

正腎上腺素劑量對診斷腸胃道出血的影響

詹正義[1*] 郭秀雯[1] 張旭超[1] 林坤榮[1] 許元昱[1]

中文摘要

這個研究主要探討腸胃道出血病患接受血管攝影檢查時降低正腎上腺素滴注量以降低腸胃道出血的假陰性率。

統計 2018 年 1 月至 2022 年 12 月總共 34 個腸胃道出血病患(19 位男性，15 位女性，平均 64.8 歲)於某醫學中心接受血管攝影檢查。這些病患平均血壓為 77/58mmHg，心跳為 121bpm。所有患者皆有接受輸血及正腎上腺素治療，將血壓控制在平均 123/87 mmHg。

緊急安排血管攝影檢查，其中有 24 位患者發現明顯腸胃道出血並施行動脈栓塞止血。10 位患者於初次血管攝影檢查時並無發現出血。我們於術中降低正腎上腺素滴注量使患者血壓控制在平均 91/61 mmHg 並再次施行血管攝影，3 位患者發現出血點並施行動脈栓塞止血。

綜合以上發現若病患因腸胃道出血接受正腎上腺素滴注治療時，若施行血管攝影檢查無發現出血點，降低正腎上腺素滴注量後再次施行血管攝影可降低血管攝影的假陰性率。

關鍵字：出血攝影、腸胃道出血、正腎上腺素

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Case Report

Retinal Arterial Macroaneurysm Presenting with Sub-internal Limiting Membrane Macular Hemorrhage: A Case Report

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ABSTRACT

Retinal arterial macroaneurysm (RAM) is an acquired retinal arterial anomaly. Patient with RAM may present with multi-layered retinal hemorrhage; sub–internal limiting membrane (sub-ILM) macular hemorrhage is an unusual presentation of RAM. We report a 75-year-old woman with hypertension who presented with sudden-onset severe blurred vision in the right eye. Ophthalmic examination revealed a dense boat-shaped macular hemorrhage, suggestive of sub-ILM retinal involvement. Spectral-domain optical coherence tomography (SD-OCT) demonstrated a sharply elevated hyperreflective lesion consistent with sub-ILM hemorrhage. The patient underwent vitrectomy surgery with internal limiting membrane (ILM) peeling and sub-ILM hemorrhage drainage. Postoperative fluorescein angiography demonstrated a pulsatile lesion along the inferotemporal arterial arcade, confirming the macular hemorrhage due to a ruptured retinal arterial macroaneurysm lesion. Visual acuity improved from preoperative counting fingers to 6/30 within one month, and follow-up SD-OCT showed marked resolution of hemorrhage. This case highlights the importance of early recognition and imaging-guided diagnosis of sub-ILM hemorrhage secondary to RAM. Timely surgical evacuation via vitrectomy with ILM peeling can facilitate rapid visual rehabilitation, minimize photoreceptor toxicity, and preserving macular function.

Keywords: Retinal arterial macroaneurysm, optical coherence tomography, sub–internal limiting membrane hemorrhage, vitrectomy

INTRODUCTION

Sub–internal limiting membrane (sub-ILM) retinal hemorrhage is a form of intraocular bleeding located between the ILM and the retinal nerve fiber layer. This anatomical position distinguishes it from other types of intraocular hemorrhage. Although it is frequently described clinically as "pre-retinal" because it appears to lie anterior to the retina, this terminology is imprecise. From an anatomical perspective, sub-ILM hemorrhage is best regarded as an intra-retinal form of hemorrhage—not truly pre-retinal.[1] Sub-ILM hemorrhage often leads to acute and sometimes severe visual impairment, particularly when it involves the macula.[2] Prolonged accumulation of blood beneath the ILM can exert toxic effects on the retina,[3] resulting in complications such as epiretinal membrane formation or persistent photoreceptor layer disruption—both of which may limit the final visual recovery even when intervention is performed at a later stage.[4] The common causes of sub-ILM retinal hemorrhage include Valsalva retinopathy, Terson syndrome, ocular trauma and blood dyscrasias.[5] It may also occur in association with systemic conditions such as hemolytic uremic syndrome, leukemia, or Kikuchi–Fujimoto disease.[6-8] Diagnosis is aided by optical coherence tomography (OCT), which can distinguish sub-ILM hemorrhage from subhyaloid hemorrhage by identifying two distinct membranes—the posterior hyaloid and the internal limiting membrane—anterior to the hemorrhage, thereby confirming its sub-ILM location.[9] Another clinical sign, termed arcus retinalis, has been described and is characterized by distinct OCT features that serve as a reliable clinical marker of sub-ILM hemorrhage.[10] Management strategies range from observation for spontaneous resolution to interventions such as Nd:YAG or 577-nm laser membranotomy, and early vitrectomy surgery, depending on the size, location and duration of the hemorrhage, and the degree of visual impairment.[4,5,11,12] Herein, we report a patient with retinal arterial macroaneurysm (RAM) complicated by massive sub-ILM macular hemorrhage who underwent early pars plana vitrectomy (PPV) surgery with drainage of sub-ILM hemorrhage, and successfully gained significant visual improvement.

CASE PRESENTATION

A 75-year-old woman presented to our outpatient service with sudden-onset blurred vision in her right eye for 10 days. She had a medical history of systemic hypertension and coronary artery disease, for which she was receiving aspirin therapy. She denied any ocular trauma history or Valsalva-like event. On presentation, her best-corrected visual acuity (BCVA) was counting fingers at 50 cm in the right eye and 6/10 in the left eye. Intraocular pressures measured 12 mmHg OD and 15 mmHg OS. Anterior segment examination was unremarkable, and multifocal intraocular lenses were present in both eyes. Fundus examination of the right eye revealed a dense, boat-shaped macular hemorrhage with multilayered components, and arcus retinalis was faintly visible at the inferior border of the hemorrhage, highly suggestive of sub-ILM and subretinal involvement (Fig. 1A). No retinal tears or detachment were identified. Spectral-domain optical coherence tomography (SD-OCT) demonstrated marked central macular thickening exceeding 900 μm, and a sharply elevated hyperreflective dome consistent with sub-ILM macular hemorrhage rather than a simple subhyaloid hemorrhage. (Fig. 2A). Because of the advanced extent of macular hemorrhage with foveal involvement, the patient was admitted for urgent surgical management. She underwent 25-gauge pars plana vitrectomy with ILM peeling, evacuation of sub-ILM hemorrhage, intravitreal injection of bevacizumab (1.25 mg), and 7.5% sulfur hexafluoride (SF_6) gas tamponade. The diagnosis was further confirmed intraoperatively, as the hemorrhage was found beneath the internal limiting membrane during surgical evacuation. On postoperative day 24, BCVA in the right eye significantly improved to 6/30. SD-OCT demonstrated complete resolution of the sub-ILM macular hemorrhage, and a reduction in central macular thickness to 294 μm (Fig. 2B). Fundus examination confirmed the substantial clearance of macular hemorrhage without any retinal traction or fibrotic change (Fig. 1B). Furthermore, fluorescein angiography (FA) revealed an early hyperfluorescent, pulsatile lesion along the inferotemporal arterial arcade, with surrounding hypofluorescence due to hemorrhagic masking, confirming the diagnosis of a ruptured RAM (Fig. 3). At postoperative day 53, the patient's visual acuity remained stable at 6/30, and fundus examination showed no recurrent hemorrhage or any signs of proliferative vitreoretinopathy.

DISCUSSION

RAM is an acquired focal dilation of retinal artery that predominantly affects elderly women and is frequently associated with systemic vascular comorbidities such as hypertension and arteriosclerosis.[13,14] Its clinical manifestations vary widely and may include multi-layered retinal hemorrhage—subretinal, intraretinal, preretinal, and sub-ILM—often making initial diagnosis challenging. In this case, a small yellow-whitish lesion at the inferotemporal arterial arcade, the

dense sub-ILM macular hemorrhage with marked hyperreflectivity dome on OCT image strongly suggested the impression of a ruptured RAM. Postoperative fluorescein angiography further demonstrated a pulsatile hyperfluorescent lesion with surrounding retinal hemorrhage, confirming the diagnosis of RAM.

The primary etiologies of sub-ILM macular hemorrhage include the followings: Valsalva retinopathy—resulting from sudden increases intrathoracic or intra-abdominal pressure (e.g., heavy lifting, forceful coughing); Terson's syndrome associated with subarachnoid hemorrhage; rupture of retinal arterial macroaneurysm, and hematologic disorders such as anemia or other blood dyscrasias.[5] Less commonly, sub-ILM hemorrhage may occur in the setting of systemic conditions such as hemolytic uremic syndrome, in which thrombotic microangiopathy and endothelial injury predispose to retinal bleeding, or Kikuchi–Fujimoto disease, where transient vasculitis, thrombophilia, or immune complex deposition may contribute to capillary fragility.[6,8] A unifying pathophysiologic mechanism of sub-ILM macular hemorrhage is disruption of the retinal microvasculature, often triggered by abrupt hemodynamic changes or coagulopathic states. Such vascular compromise allows blood to dissect beneath the ILM, with preferential accumulation at macular region where structural and gravitational factors promote pooling of hemorrhage.

Differentiating sub-ILM hemorrhage from subhyaloid hemorrhage is clinically important but may be challenging because both may appear as sharply demarcated premacular hemorrhage on fundus examination. Previous reports have shown that OCT is particularly helpful when two distinct membranes anterior to the hemorrhage can be identified, representing the posterior hyaloid and the ILM, thereby supporting sub-ILM localization.[9] In addition, a glistening surface reflex and the presence of 'arcus retinalis,' a yellowish-white arc at the outer margin of the hemorrhage with corresponding peg-like OCT features, have been described as useful clues favoring sub-ILM hemorrhage.[10] In our case, the preoperative OCT findings were more consistent with sub-ILM hemorrhage. Moreover, the fundus examination showed the presence of a glistening surface reflex and arcus retinalis was faintly visible at the inferior border of the hemorrhage in Figure 1A, providing an additional clinical clue. The diagnosis was further confirmed intraoperatively when the hemorrhage was found beneath the ILM during vitrectomy and surgical evacuation.

The management of sub-ILM hemorrhage aims to optimize visual outcomes and minimize retinal damage, with treatment strategies tailored to the size and location of hemorrhage, etiology, and impact on visual acuity. Observation may be appropriate for small, non-foveal hemorrhage, as spontaneous resorption can occur over several weeks to months. However, persistent or vision-threatening hemorrhage often requires active intervention to prevent the risk of hemosiderin toxicity and irreversible retinal injury. Nd: YAG laser hyaloidotomy is a minimally invasive option for evacuating subhyaloid or sub-ILM hemorrhages, particularly in juxtafoveal cases. It offers rapid visual recovery but carries the risk of complications, including macular hole formation and retinal injury.[11] Laser membranotomy using 577-nm or 532-nm wavelength has also demonstrated high efficacy in facilitating drainage of hemorrhage into the vitreous cavity, resulting in prompt visual improvement. A recent study reported a 94.7% success rate with 577-nm laser membranotomy, although complications such as macular holes, epiretinal membranes, and sub-ILM cavities have been documented and necessitate careful follow-up.[15] The 532-nm laser has likewise shown effectiveness, particularly when Nd:YAG photodisruption is unsuccessful, and may offer a safer, more controlled energy profile in selected cases.[16] For dense or fovea-involving macular hemorrhages, PPV surgery with ILM peeling is often indicated. This approach allows direct removal of blood and its breakdown products, reducing the likelihood of secondary epiretinal membrane formation and improving visual prognosis.[11,12] Although ILM peeling is traditionally performed, recent alternatives include non-peeling techniques designed to preserve the foveal ILM and potentially decrease the risk of postoperative full-thickness macular hole formation.[12] Pneumatic displacement with intraocular gas tamponade, such as perfluoropropane (C3F8) gas, represents a less invasive option for selected patients—particularly those requiring rapid recovery or who are unable to undergo surgery. When combined with prone positioning, this method has yielded favorable results in conditions such as dengue maculopathy–related sub-ILM hemorrhage.[17] Ultimately, treatment selection should be individualized based on the patient's clinical status, visual need, and the characteristics of the hemorrhage. Early intervention is generally associated with improved visual outcomes and a reduced risk of long-term complication. In this case, vitrectomy with ILM peeling and sub-ILM hemorrhage drainage achieved the substantial anatomical and functional recovery.

*This study was approved by the Institutional Ethics Review Board on 2026-04-09 (IRB No.: 20260212R)

CONCLUSION

The clinical presentation of Sub-ILM macular hemorrhage secondary to ruptured RAM poses both diagnostic and therapeutic challenges, necessitating careful differentiation from other macular pathologies. Prompt multimodal imaging study—including OCT and fluorescein angiography—is crucial for establishing an accurate diagnosis. In significantly vision-threatening cases, particularly those with foveal involvement, vitrectomy with ILM peeling remains a safe and effective treatment option. Early surgical intervention promotes rapid visual rehabilitation, mitigates the risk of long-term photoreceptor damage, and allows identification of underlying vascular abnormalities to guide the subsequent management.

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FIGURE AND FIGURE LEGENDS

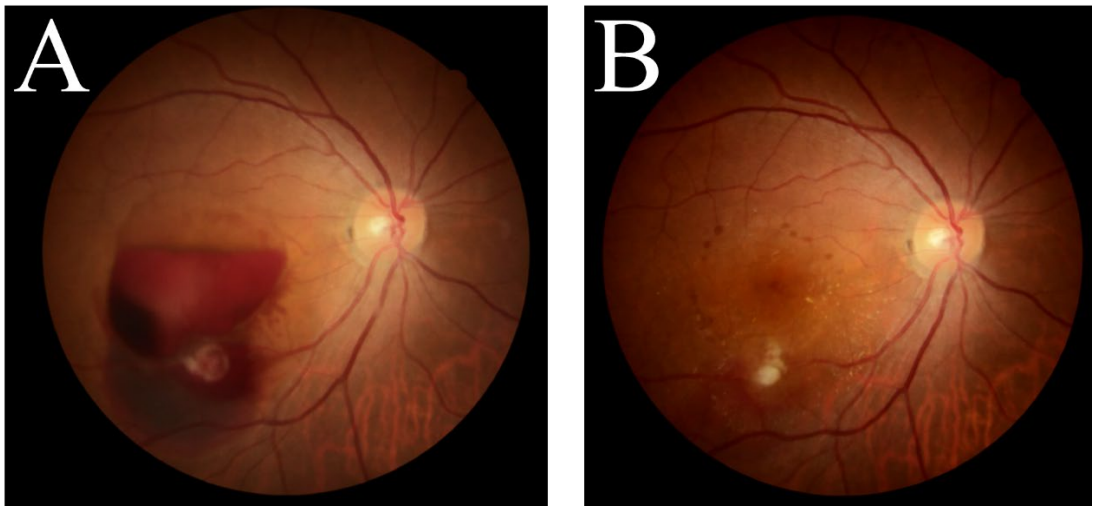


Figure 1. Fundus photography demonstrated boat-shaped macular hemorrhage with dense sub-internal limiting membrane (sub-ILM) component, the presence of a glistening surface reflex and arcus retinalis was faintly visible at the inferior border of the hemorrhage preoperatively (A), and substantial resolution of hemorrhage following vitrectomy and drainage of sub-ILM hemorrhage (B).

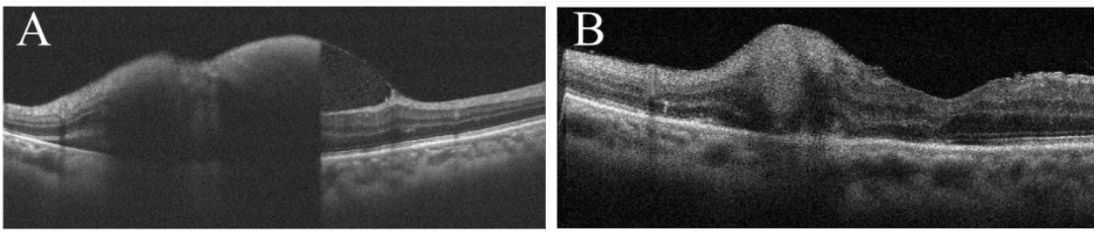


Figure 2. Spectral-domain optical coherence tomography showed a sharply elevated hyperreflective dome consistent with sub-ILM macular hemorrhage with thick sub-internal limiting membrane (sub-ILM) component preoperatively (A), and marked resolution of hemorrhage following vitrectomy surgery with ILM peeling and drainage of sub-ILM hemorrhage (B).

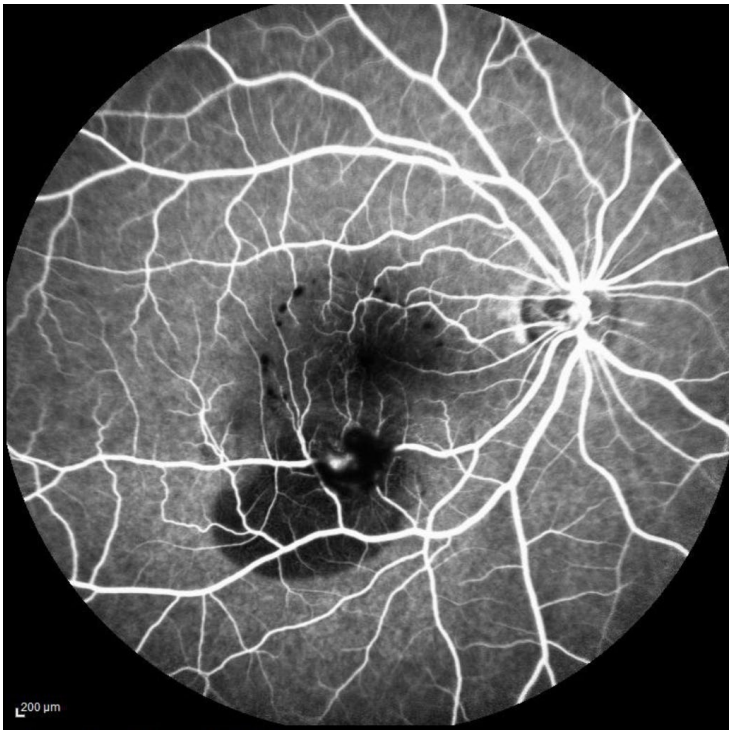


Figure 3. Fluorescein angiography (FA) showed an early hyperfluorescent, pulsatile lesion at the inferotemporal arterial arcade, accompanied by surrounding hypofluorescence due to hemorrhagic masking, confirming the diagnosis of a ruptured retinal arterial macroaneurysm.



Retinal Macroaneurysm induced Macular Hemorrhage

Retinal Arterial Macroaneurysm Presenting with Sub-internal Limiting Membrane Macular Hemorrhage: A Case Report

以黃斑部內界膜下出血為臨床表現之視網膜巨動脈瘤：病例報告

郭曜儀[1]　鄭成國[1,2,4]　楊昌叔[1,3*]

中文摘要

視網膜巨動脈瘤為一種後天性視網膜動脈病變，可導致多層次視網膜出血；其中黃斑部內界膜下出血屬於相對少見之臨床表現。本文報告一位 75 歲、合併高血壓之女性，因右眼突發性嚴重視力模糊就醫。眼科檢查發現黃斑區有濃厚、舟狀的出血，高度懷疑病灶涵蓋至內界膜下區域。頻譜域光學同調斷層掃描顯示黃斑區呈急峻隆起之高反射性病灶，影像特徵與內界膜下出血一致。患者接受了玻璃體切除手術合併內界膜剝除及內界膜下出血之引流。手術後螢光血管攝影檢查於下顳側動脈發現一搏動性病灶，據此確立黃斑部出血為視網膜巨動脈瘤破裂所致。術後一個月病患視力由術前僅能辨指數進步至 6/30，後續頻譜域光學同調斷層掃描之追蹤顯示出血顯著吸收。此病例報告強調對於視網膜巨動脈瘤併發之內界膜下出血，早期辨識及結合影像之診斷策略至關重要；及時施行玻璃體切除手術合併內界膜剝除以清除出血，可加速視力復原、降低血液分解產物對感光細胞之毒性影響，並有助於維持黃斑部功能。

關鍵字：視網膜巨動脈瘤、光學同調斷層掃描、內界膜下出血、玻璃體切除術

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