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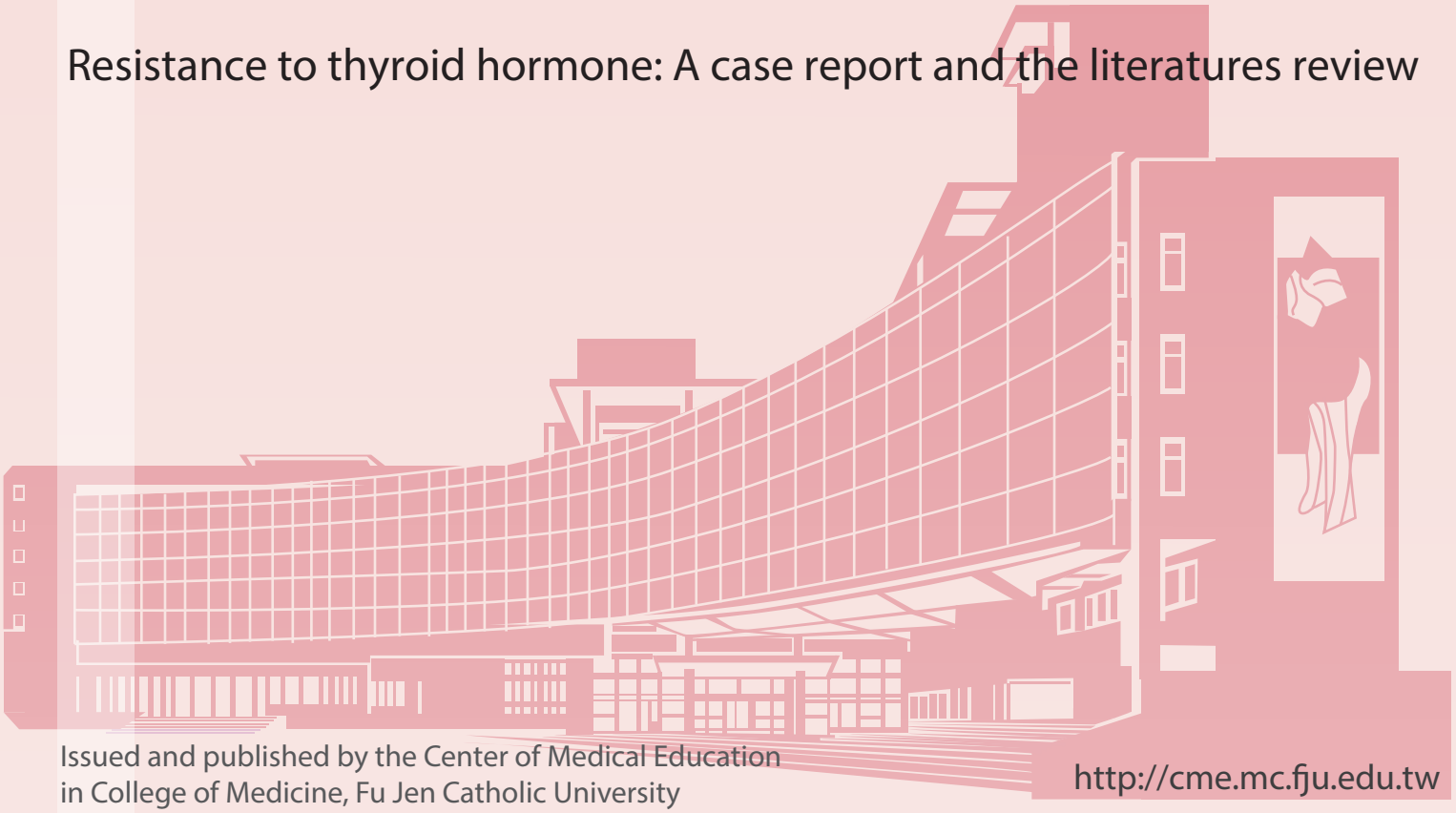

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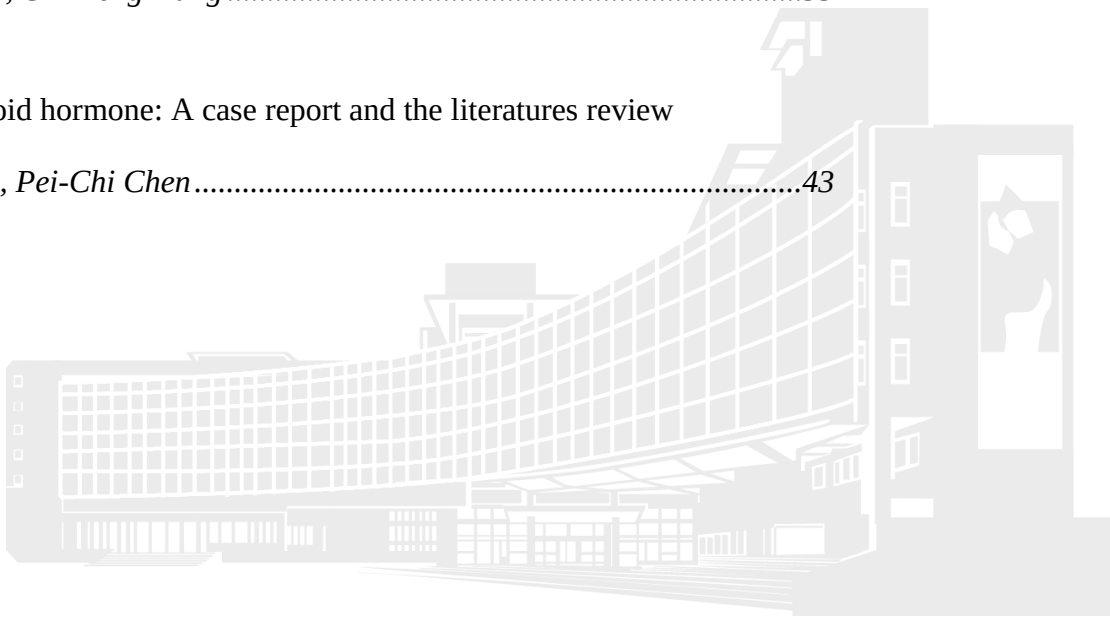

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Original Research Article

TRIP13 as a Potential Prognostic Marker and Therapeutic Target in Acute Myeloid Leukemia

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ABSTRACT

Background: Acute myeloid leukemia (AML) is a genetically heterogeneous hematologic malignancy characterized by uncontrolled proliferation of immature myeloid cells. Despite advancements in targeted therapies, long-term survival rates remain poor. Identifying novel biomarkers is essential for improving prognosis and guiding treatment. ***Methods:*** We performed an integrative analysis of three publicly available Gene Expression Omnibus (GEO) datasets (GSE121169, GSE149237, and GSE63270) to identify differentially expressed genes (DEGs) between AML and healthy control samples. Functional enrichment analyses, including Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, Cancer Hallmarks, protein-protein interaction (PPI) network analysis (STRING and Cytoscape), and hub gene identification (Degree and Maximum Neighborhood Component (MNC) algorithms) were performed. Prognostic impact was assessed using Kaplan–Meier Plotter and UCSC Xena. TRIP13 expression was further analyzed in relation to FLT3, PML/RARA, and NRAS mutation status in The Cancer Genome Atlas (TCGA) cohorts. ***Results:*** We identified 118 overlapping DEGs enriched in mitotic regulation and genome instability pathways. Among ten consensus hub genes, only high TRIP13

expression was significantly associated with worse overall survival. TRIP13 levels were elevated in NRAS-mutant AML and showed context-dependent prognostic effects: predicting poor survival in NRAS wild-type patients but better outcomes in NRAS-mutant cases. Conclusion: TRIP13 is a context-dependent prognostic biomarker in AML, potentially improving risk stratification beyond current mutation-based models. These findings highlight TRIP13 as a candidate for targeted therapy, warranting further mechanistic validation. Further functional studies are warranted to clarify its mechanistic role in leukemogenesis and treatment response.

Keywords: Acute myeloid leukemia (AML), TRIP13, bioinformatics, prognostic biomarker

INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive and genetically heterogeneous hematologic malignancy characterized by clonal proliferation of myeloid precursors and a blockade in their differentiation. Although AML accounts for only 1% of all cancers, it is the most common acute leukemia in adults and remains associated with poor outcomes, especially in older patients, where the median age at diagnosis exceeds 65 years[1]. Current treatment strategies for AML, such as cytotoxic chemotherapy and hematopoietic stem cell transplantation, often yield suboptimal outcomes in older patients or those with high-risk profiles due to toxicity, drug resistance, and disease recurrence[2]. With a five-year survival rate below 30%, there is a pressing need for novel prognostic biomarkers and innovative therapeutic approaches to enhance clinical outcomes across diverse AML subtypes.

Substantial progress in next-generation sequencing (NGS) has uncovered numerous recurrent somatic mutations involved in AML pathogenesis, including those in FLT3, NPM1, CEBPA, TP53, and ASXL1. These genetic alterations have informed current classification systems and risk stratification models such as the European LeukemiaNet (ELN) guidelines[3]. However, even with molecularly guided treatment, outcomes for many patients—particularly those without favorable genetic profiles—remain unsatisfactory. Moreover, many current biomarkers and drug targets offer limited clinical utility due to intratumoral heterogeneity, drug resistance, and a lack of consistent prognostic relevance[4, 5].

Dysregulation of mitotic cell cycle processes, including spindle assembly and chromosome segregation, is a hallmark of leukemogenesis and genomic instability. Emerging evidence highlights the critical roles of genes encoding kinesins, topoisomerases, aurora kinases, and ribonucleotide reductase subunits in tumor progression and treatment resistance across various solid tumors[6-9]. These proteins regulate essential mitotic and DNA replication checkpoints, positioning them as promising targets for anticancer therapies. However, their roles in AML, particularly regarding expression patterns, mutation frequencies, and clinical associations, remain underexplored.

In this study, we utilized an integrative bioinformatics approach to identify and validate key prognostic genes in AML. We analyzed three publicly available datasets from the Gene Expression Omnibus (GEO) to identify differentially expressed genes (DEGs) between AML and normal samples. Through protein-protein interaction (PPI) network analysis, hub gene identification, and survival analysis using Kaplan-Meier plotter and UCSC Xena, we identified a subset of genes significantly correlated with overall survival and genomic alterations in AML. Our results reveal a group of underexpressed, prognostically favorable genes that may serve as novel therapeutic targets or biomarkers. These findings offer potential strategies to address challenges in AML management, particularly in overcoming drug resistance and disease heterogeneity.

MATERIALS AND METHODS

2.1. Data Acquisition and Preprocessing

Three publicly available gene expression datasets related to acute myeloid leukemia (AML) were retrieved from the NCBI Gene Expression Omnibus (GEO) database: GSE121169, GSE149237, and GSE63270. The GSE121169 dataset, comprising 7 normal and 12 AML samples, was generated using the Illumina HiSeq 2500 platform (GPL16791) and released on De-

cember 23, 2023. GSE149237 included 4 normal and 5 AML samples and was produced using the Illumina HiSeq 4000 platform (GPL20301) on October 25, 2024. GSE63270 consisted of 42 normal and 62 AML samples and was based on the Affymetrix Human Genome U133 Plus 2.0 Array platform (GPL17810), released on November 14, 2018. Raw expression data from each dataset were normalized and analyzed using the GEO2R online tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/), which applies the limma package for differential gene expression analysis. Genes with an absolute $\log_2$ fold change ($|\log_2 FC| \geq 1$ and adjusted $p < 0.01$ (Benjamini–Hochberg correction) were considered differentially expressed.

2.2. Identification of Common DEGs

To identify consistently dysregulated genes across all three datasets, Venn diagram analysis was performed using the InteractiVenn (https://www.interactivenn.net/). DEGs common to all three datasets were selected for subsequent functional and network analysis.

2.3. Functional Enrichment Analysis

Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted using the ShinyGO v0.82 web tool (https://bioinformatics.sdstate.edu/go/). Categories including biological process (BP), molecular function (MF), and cellular component (CC) were enriched with a false discovery rate (FDR) < 0.05[10-12]. Cancer hallmark associations were evaluated using the Cancer \\

Hallmarks Analytics Tool (https://cancerhallmarks.com/), with adjusted p < 0.01 as the cutoff for significance[13].

2.4. Protein–Protein Interaction (PPI) Network Construction

he Search Tool for the Retrieval of Interacting Genes (STRING v12.0; https://string-db.org/) was used to construct the PPI network of the 118 common DEGs, applying a confidence score > 0.4 as the interaction threshold[14, 15]. The resulting network was imported into Cytoscape software (v3.10.2) for visualization and further analysis.

2.5. Hub Gene Identification

Within Cytoscape, the CytoHubba plugin was used to determine hub genes based on two topological algorithms: Degree and Maximum Neighborhood Component (MNC)[16, 17]. Genes ranked in the top 10 by both methods were intersected using a Venn diagram to identify robust hub genes.

2.6. Genomic Expression and Prognostic Analysis of Hub Genes in AML

To evaluate the transcriptional profiles of hub genes in acute myeloid leukemia (AML), we utilized the UCSC Xena platform (https://xena.ucsc.edu), which integrates publicly available genomic and phenotypic data from large-scale cancer studies, including TCGA and Genomic Data Commons (GDC) cohorts [18, 19]. Gene expression levels were compared between AML samples and corresponding normal tissues to assess differential expression patterns. Prognostic significance of hub genes was assessed using the Kaplan–Meier plotter (https://kmplot.com/analysis/), selecting AML-specific survival data from the blood malignancies section.[20, 21] Patients were divided into high and low expression groups based on the median expression, and differences in survival were evaluated using the log-rank test. A p value < 0.05 was considered statistically significant.

2.7. Expression Comparison Between AML and Normal Samples

Expression levels of key hub genes were compared between AML and normal controls using expression values from the TCGA datasets. Statistical analysis was performed using unpaired t-tests, with $p < 0.05$ considered significant.

2.8. Statistical Analysis

Differential expression in GEO2R was calculated using limma-based moderated t-tests, with adjusted p-values corrected using the Benjamini–Hochberg method to control the false discovery rate (FDR). A gene was considered significantly differentially expressed if $|\log_2 FC| \geq 1$ and adjusted $p < 0.01$. Survival curves were generated via the Kaplan–Meier method, and differences between groups were compared using the log-rank (Mantel–Cox) test. For expression comparisons between AML and control groups, unpaired two-tailed Student's t-tests were applied unless otherwise specified. A p value < 0.05 was considered statistically significant.

RESULTS

3.1. Identification of a Robust Gene Signature for Acute Myeloid Leukemia through Multi-Dataset Transcriptomic Analysis

To investigate therapeutic challenges in acute myeloid leukemia (AML), we sought to identify novel target genes associated with disease progression and potential therapeutic or

prognostic biomarkers. We retrieved three transcriptomic datasets from the Gene Expression Omnibus (GEO) database: GSE121169 (7 normal vs. 12 AML samples), GSE149237 (4 normal vs. 5 AML samples), and GSE63270 (42 normal vs. 62 AML samples) (Figure 1A). Differential gene expression analysis was conducted using the GEO2R platform, with significance thresholds set at an adjusted p-value < 0.01 and $|\log_2 FC| \geq 1$. This analysis identified 2,049 differentially expressed genes (DEGs) in GSE149237, 3,125 in GSE121169, and 1,747 in GSE63270. Volcano plots were generated to visualize significantly upregulated (red) and downregulated (blue) genes in each dataset (Figures 1B–D). To ensure robustness and minimize dataset-specific bias, we employed a Venn diagram approach to identify overlapping DEGs across all three datasets, resulting in 118 consistently dysregulated genes in AML (Figure 1E). These shared DEGs represent a robust gene signature associated with AML pathogenesis, offering potential insights into leukemogenesis, therapy resistance, and novel molecular targets for clinical intervention.

3.2. Functional Enrichment Analysis Highlights Cell Cycle and Genome Instability Pathways Associated with AML-Related DEGs

To further explore the biological relevance of the 118 consistently dysregulated genes identified across AML datasets, we conducted functional enrichment analyses using multiple bioinformatics platforms. Using the Cancer Hallmark database, these genes were found to be significantly enriched in pathways associated with genome instability, a hallmark of malignant transformation ($p < 0.01$) (Figure 2A). Gene Ontology (GO) analysis was then performed via the ShinyGO 0.82 platform to assess the biological processes (BP), cellular components (CC), and molecular functions (MF) in which these DEGs were involved. In the biological process category, DEGs were significantly enriched in mitosis- and cell cycle-related pathways, including regulation of mitotic nuclear division, chromosome segregation, organelle fission, and cell cycle phase transitions (Figure 2B). In the cellular component domain, DEGs were localized to structures central to chromosome segregation and mitotic progression, such as the chromosome passenger complex, spindle apparatus, centrosome, midbody, kinetochore, and cytoskeletal elements (Figure 2C). Within the molecular function category, the genes were predominantly involved in microtubule motor activity, ATP-dependent chromatin and cytoskeletal protein binding, and various nucleotide-binding functions (Figure 2D). Consistent with these observations, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed significant enrichment in the cell cycle pathway, further supporting the role of these DEGs in dysregulated cell division (Figure 2E). Collectively, these results suggest that the 118 core DEGs are primarily involved in cell proliferation and chromosomal instability, highlighting their potential contribution to AML progression and therapeutic resistance.

3.3. Construction of Protein–Protein Interaction Network and Identification of Key Hub Genes in AML

To uncover central regulators among the 118 consistently dysregulated genes, we constructed a protein–protein interaction (PPI) network using the STRING database, which integrates known and predicted physical and functional interactions. The resulting network revealed a highly interconnected set of proteins potentially involved in AML pathogenesis (Figure 3A). We imported the STRING-derived interaction network into Cytoscape for further topological analysis and clustering (Figure 3B). Hub genes were identified from the PPI network using the Degree and Maximum Neighborhood Component (MNC) algorithms implemented in the CytoHubba plugin of Cytoscape. To identify high-confidence hub genes, we applied two ranking algorithms, Degree and Maximum Neighborhood Component (MNC), via the CytoHubba plugin. The top 10 hub genes identified by the Degree algorithm were: CDK1, TRIP13, KIF23, RRM2, KIF11, TOP2A, CENPF, MAD2L1, BUB1B, and AURKB (Figure 3C). The MNC algorithm yielded an overlapping set of genes: CDK1, BUB1B, KIF11, TRIP13, KIF23, TOP2A, AURKB, MAD2L1, CENPF, and RRM2 (Figure 3D). To ensure analytical robustness, we identified the intersection of these two ranking methods via Venn analysis, which revealed 10 consensus hub genes: CDK1, TRIP13, KIF11, BUB1B, AURKB, KIF23, TOP2A, RRM2, MAD2L1, and CENPF (Figures 3E–F). These genes, which are involved in cell cycle regulation, mitotic checkpoint control, and chromosomal stability, were prioritized for further investigation into their role in AML progression and therapeutic resistance.

3.4. TRIP13 Expression Is Uniquely Associated with Poor Prognosis in AML Patients

To examine the clinical relevance of the identified hub genes, we examined their expres-

sion profiles and prognostic significance in AML using the UCSC Xena platform (https://xena.ucsc.edu), which integrates transcriptomic and survival data from GDC and TCGA cohorts. Expression analysis revealed that the ten hub genes displayed relatively consistent patterns across AML samples, with several genes showing coordinated upregulation or downregulation (Figure 4A). We next performed Kaplan–Meier survival analyses to investigate the impact of gene expression on overall survival (OS) in AML patients. Among the ten hub genes, only high expression of TRIP13 was significantly associated with shorter OS (p = 0.0483) (Figure 4B). In contrast, the expression levels of the remaining nine genes, CDK1 (p = 0.7033), KIF11 (p = 0.5680), BUB1B (p = 0.7734), AURKB (p = 0.8391), KIF23 (p = 0.9861), TOP2A (p = 0.4129), RRM2 (p = 0.8698), MAD2L1 (p = 0.9107), and CENPF (p = 0.2153), were not significantly associated with OS (Figures 4C–K). These findings highlight TRIP13 as a uniquely prognostic gene among the identified hubs, suggesting a potential role in disease progression and underscoring its value as a candidate biomarker for further clinical and functional validation in AML.

3.5. TRIP13 expression is modulated by RAS mutation status and predicts favorable prognosis in NRAS-mutant AML

Given the diverse genetic landscape of AML, we examined whether TRIP13 expression correlates with common molecular abnormalities, including FLT3 mutations, PML/RARA fusion, and RAS pathway activation, using TCGA datasets[22-25]. TRIP13 transcript levels did not differ significantly between patients with or without FLT3 mutations (Figure 5A), nor between those with or without PML/RARA fusions (Figure 5B). However, patients with RAS mutations exhibited significantly higher TRIP13 expression compared to those with wild-type RAS ($p < 0.05$) (Figure 5C). To further evaluate the interaction between TRIP13 expression and RAS mutation status, we performed stratified survival analysis using KM Plotter. Although KRAS-mutant patients were insufficient for survival modeling, in KRAS wild-type patients, high TRIP13 expression was associated with a hazard ratio (HR) of 1.2 but did not reach statistical significance (p = 0.089) (Figure 5D). Intriguingly, in patients with NRAS wild-type, high TRIP13 expression was associated with significantly worse overall survival (HR = 1.25, p = 0.045) (Figure 5E). In contrast, among NRAS-mutant patients, high TRIP13 expression correlated with significantly improved survival (HR = 0.33, p = 0.00028) (Figure 5F). These findings suggest that the prognostic significance of TRIP13 may depend on the RAS mutational context, particularly within NRAS subgroups. TRIP13 thus holds potential as a subtype-specific prognostic biomarker and may serve as a molecular basis for personalized therapeutic strategies, especially in the development of gene- or pathway-targeted interventions for AML.

DISCUSSION

Acute myeloid leukemia (AML) is a genetically and clinically heterogeneous hematologic malignancy, primarily driven by the accumulation of somatic mutations in hematopoietic stem and progenitor cells that disrupt normal myeloid differentiation and promote clonal expansion[1]. Despite advances in cytogenetics, molecular profiling, and targeted therapy, treatment resistance and relapse remain common, particularly among older patients or those with high-risk genetic aberrations such as TP53 or complex karyotypes[2, 5]. Consequently, the identification of novel molecular drivers and prognostic biomarkers remains critical for improving risk stratification and guiding therapeutic decisions in AML.

In this study, we identified 118 consistently dysregulated genes across three independent AML transcriptomic datasets. Functional enrichment analyses revealed that these genes were highly involved in cell cycle regulation, mitotic progression, and chromosomal segregation, key biological processes often dysregulated in leukemogenesis. Protein-protein interaction (PPI) network analysis and CytoHubba-based ranking identified ten hub genes, among which TRIP13 emerged as a unique candidate with significant clinical relevance. TRIP13 was the only hub gene whose high expression was significantly associated with worse overall survival (OS) in AML patients (p = 0.0483), highlighting its potential role in AML pathophysiology and prognosis.

Interestingly, higher TRIP13 expression within AML patients was significantly associated with worse overall survival. This finding highlights the potential clinical relevance of intratumoral TRIP13 expression levels and suggests that overexpression in certain AML subgroups may contribute to disease aggressiveness. In other malignancies, TRIP13 has been implicated in key oncogenic processes, including DNA repair, spindle assembly checkpoint control, and chromosomal stability, which promote tumor survival under replication stress or thera-

py-induced DNA damage[26-28]. A similar role in AML may explain why elevated TRIP13 expression correlates with poorer prognosis in specific molecular contexts.

Moreover, TRIP13 expression was significantly influenced by underlying genetic context. Although no significant differences were found in TRIP13 levels between patients with or without FLT3 mutations or PML/RARA fusions, patients with NRAS mutations exhibited significantly elevated TRIP13 expression. Prognostically, high TRIP13 expression predicted significantly worse OS in NRAS wild-type patients, while paradoxically associating with better OS in NRAS-mutant patients. These results suggest potential cross-talk between RAS signaling and TRIP13-mediated pathways, warranting further mechanistic investigation[29, 30]. Notably, FLT3 remains one of the most actionable AML mutations with available targeted inhibitors[31, 32], yet our findings suggest TRIP13 expression may stratify risk independent of FLT3 status.

Clinically, these findings position TRIP13 as a potential prognostic biomarker and molecular target for therapeutic development. Given the increasing adoption of precision medicine in AML, particularly through the integration of FLT3, IDH1/2, and BCL-2 inhibitors, our data underscore the importance of expanding the biomarker landscape to include additional genes such as TRIP13, which may provide prognostic value even in patients lacking currently actionable mutations[31, 33, 34]. Given the increasing adoption of precision medicine in AML, integrating TRIP13 expression with established genetic markers such as FLT3, IDH1/2, and NRAS may enhance risk stratification and guide more personalized therapeutic approaches. Furthermore, the differential association of TRIP13 expression with overall survival in relation to NRAS mutation status suggests that integrated biomarker models combining both genetic mutations and gene expression levels may offer improved risk stratification and personalized treatment guidance in AML.

This study has several limitations. First, our analyses were based entirely on publicly available transcriptomic datasets, and therefore rely on retrospective, correlative observations rather than prospective validation. Second, certain patient subgroups, such as those with KRAS mutations, had limited sample sizes, which restricted statistical power for some associations. Third, we did not perform cell-based or animal experiments to validate the mechanistic role of TRIP13 in AML proliferation, survival, or treatment response. Future studies should address these limitations by incorporating larger patient cohorts, in vitro and in vivo functional assays, and mechanistic investigations into TRIP13-mediated pathways, particularly in the context of RAS signaling and DNA damage response, to establish its potential as a therapeutic target.

CONCLUSIONS

Acute myeloid leukemia remains a challenging malignancy with poor prognosis despite targeted therapies. Our study identifies TRIP13 as a novel prognostic biomarker, with expression linked to survival outcomes and NRAS mutation status. These findings may refine risk stratification and inform future AML-targeted treatment strategies.

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CRediT authorship contribution statement

Kuan-Ting Lu: Conceptualization, Funding acquisition, Methodology, Writing – original draft. Tsung-Ming Chang: Data curation, Methodology, Project administration, Investigation. Ji-Fan Lin: Formal analysis, Methodology, Software, Resources. Ju-Fang Liu: Methodology, Formal analysis, Project administration, Investigation. Chi-Jen Chang: Conceptualization, Formal analysis, Investigation, Writing – review & editing.

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FIGURE AND FIGURE LEGENDS

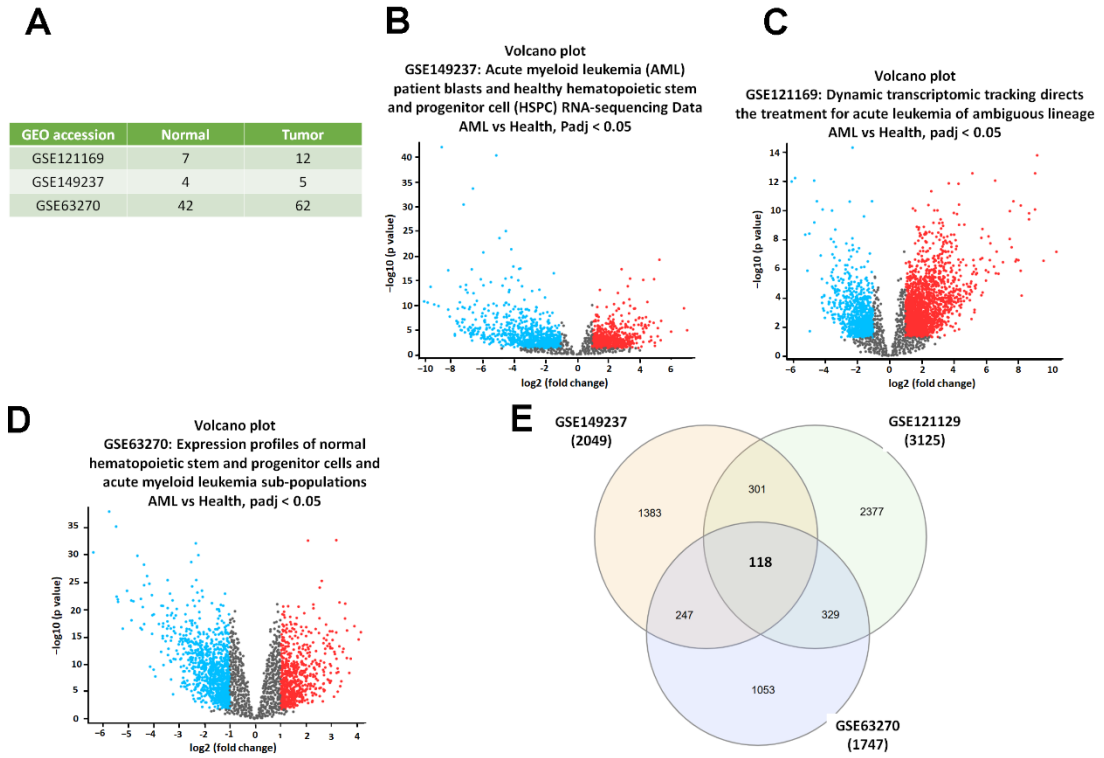


Figure 1. Identification of differentially expressed genes (DEGs) in AML across three GEO datasets. (A) Normal-derived and AML-derived sample sizes for the GSE121169 (7 normal vs. 12 AML samples), GSE149237 (4 normal vs. 5 AML samples), and GSE63270 (42 normal vs. 62 AML samples) datasets. (B–D) Volcano plots of DEGs from GSE149237, GSE121169, and GSE63270. DEGs were identified using GEO2R with cutoff values of $|\log_2 FC| \geq 1$ and adjusted $p < 0.01$ (Benjamini–Hochberg correction). Blue indicates significantly down-regulated DEGs, and red indicates significantly up-regulated DEGs. (E) Venn diagram showing overlapping DEGs among the three datasets.

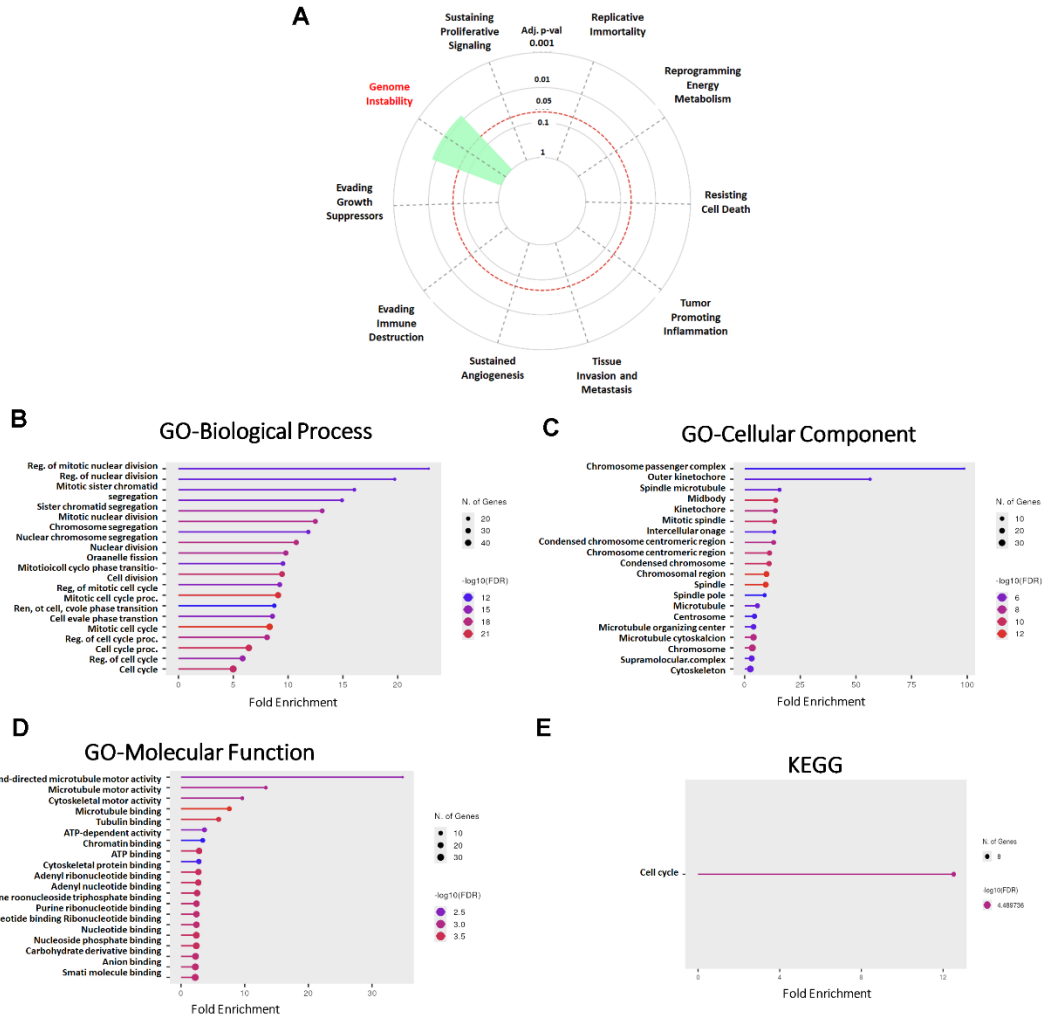
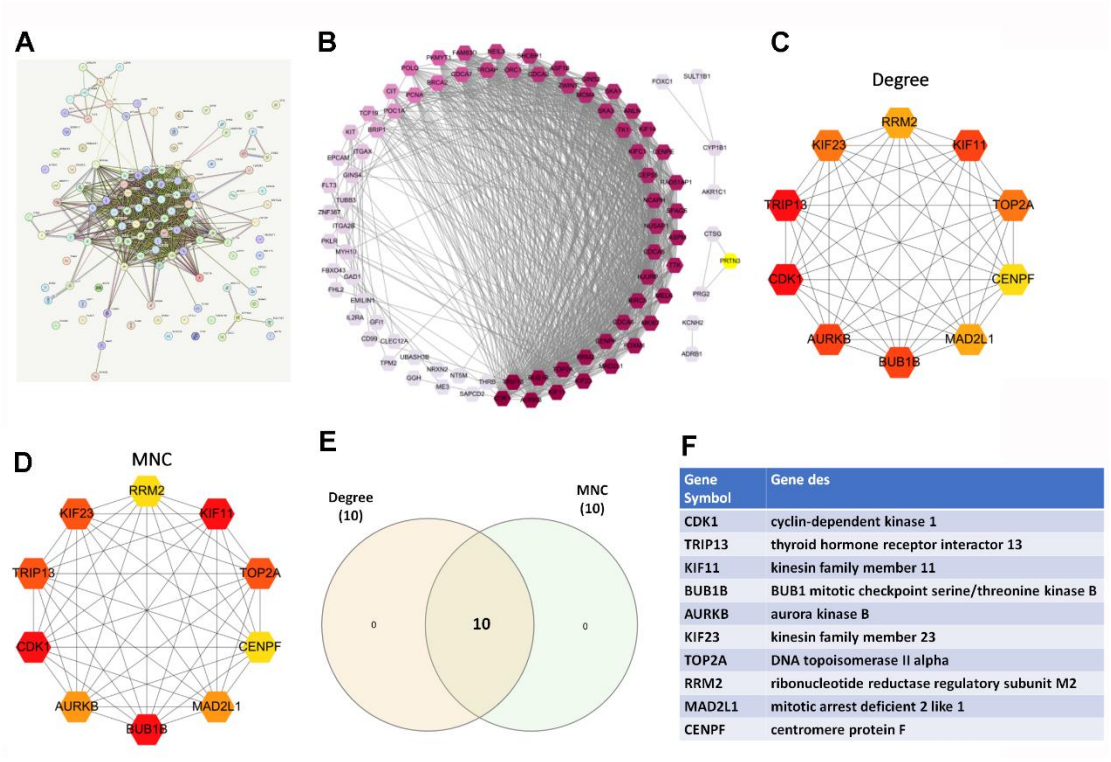


Figure 2. Functional enrichment analysis of the 118 overlapping DEGs. (A) Cancer hallmark gene set enrichment analysis using the Cancer Hallmarks Analytics Tool. (B–D) Gene Ontology (GO) analysis of biological process (BP), cellular component (CC), and molecular function (MF) using the ShinyGO 0.82 platform. (E) KEGG pathway enrichment analysis performed via ShinyGO. Statistical significance was assessed using FDR < 0.05.



Gene Symbol	Gene des
CDK1	cyclin-dependent kinase 1
TRIP13	thyroid hormone receptor interactor 13
KIF11	kinesin family member 11
BUB1B	BUB1 mitotic checkpoint serine/threonine kinase B
AURKB	aurora kinase B
KIF23	kinesin family member 23
TOP2A	DNA topoisomerase II alpha
RRM2	ribonucleotide reductase regulatory subunit M2
MAD2L1	mitotic arrest deficient 2 like 1
CENPF	centromere protein F

Figure 3. Identification of hub genes through protein–protein interaction (PPI) network analysis. (A) PPI network of 118 DEGs constructed using the STRING database (confidence score > 0.4). (B) PPI clustering visualized using Cytoscape. (C–D) Top 10 hub genes identified using the Degree and MNC algorithms via CytoHubba plugin in Cytoscape. (E) Venn diagram showing overlapping hub genes from both algorithms. (F) List of the 10 consensus hub genes with their functional annotations.

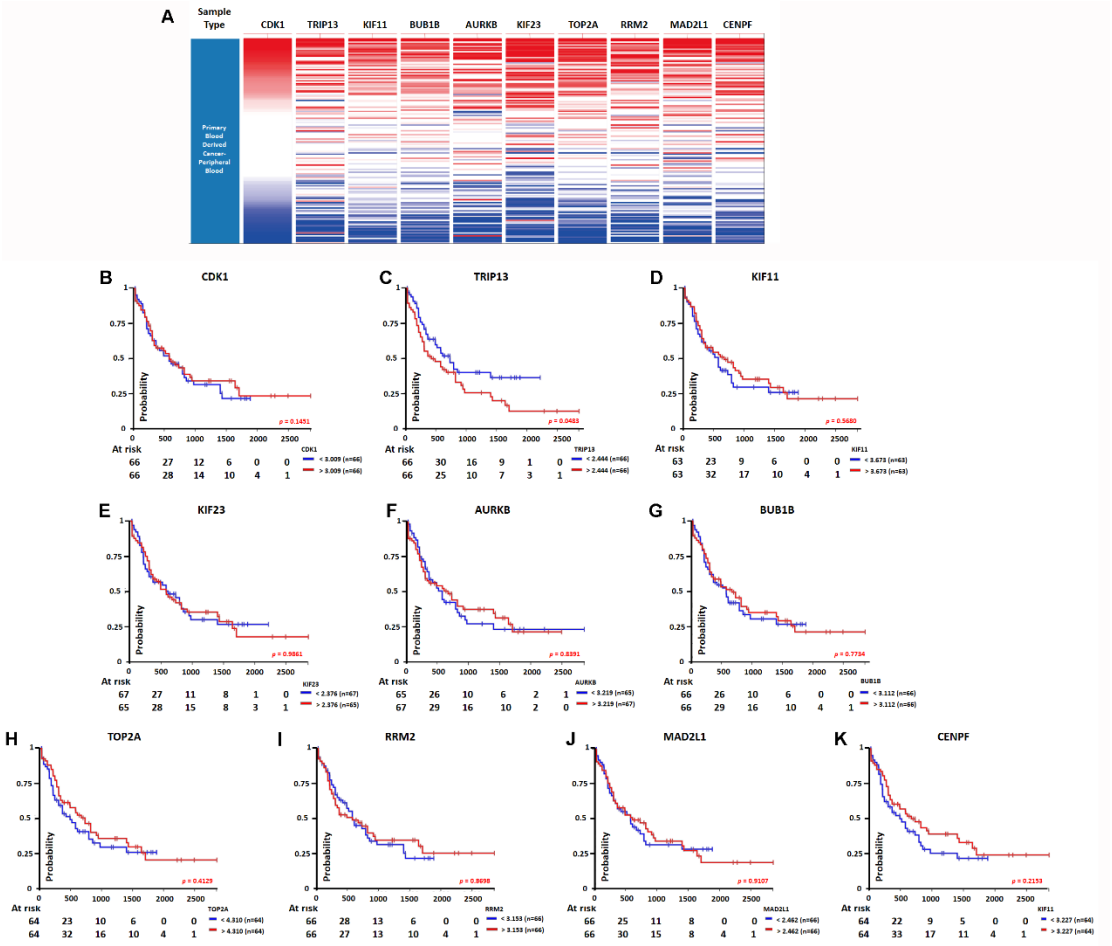


Figure 4. High TRIP13 expression is associated with poor overall survival in AML patients. (A) Box plot of expression levels of the 10 hub genes in AML samples compared to normal controls, based on TCGA and GDC cohorts from the UCSC Xena platform. (B–K) Kaplan–Meier survival curves analysis of overall survival (OS) for each hub gene using the Kaplan–Meier Plotter tool. Patients were divided by auto-selected best cutoff values. Statistical significance was calculated using the log-rank test ($p < 0.05$).

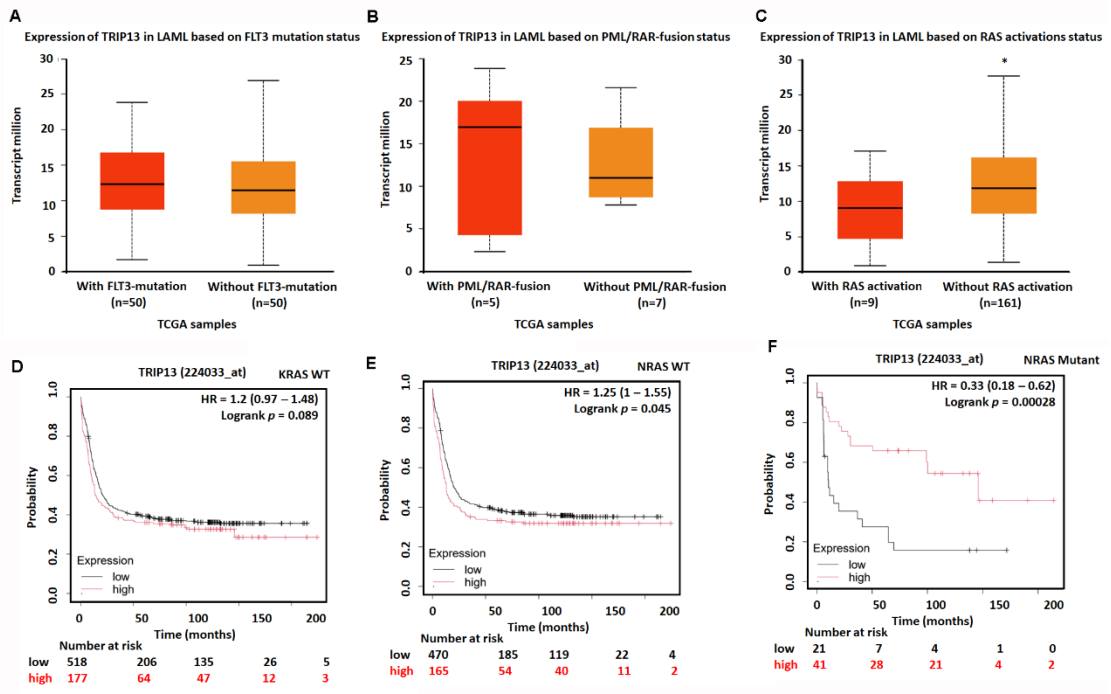


Figure 5. TRIP13 expression is elevated in RAS wild-type AML but predicts better survival in NRAS-mutant patients. (A–C) Box plots comparing TRIP13 expression in AML patients with or without FLT3 mutations, PML/RARA fusions, and NRAS mutations, analyzed using the UALCAN platform (TCGA AML dataset). (D–F) Kaplan–Meier overall survival (OS) curves for TRIP13 expression in KRAS wild-type, NRAS wild-type, and NRAS-mutant patients using Kaplan–Meier Plotter. Log-rank test was used to determine statistical significance. *$p < 0.05$.

TRIP13 as a Potential Prognostic Marker and Therapeutic Target in Acute Myeloid Leukemia

TRIP13 作為急性骨髓性白血病潛在預後標誌物與治療靶點的探討

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中文摘要

背景：急性骨髓性白血病（AML）具高度基因異質性，儘管治療進展，長期存活率仍不理想，亟需新型預後標誌物以改善治療策略。**方法：**整合三個 GEO 資料集（GSE121169、GSE149237、GSE63270），篩選 AML 與健康對照間的差異表現基因（DEGs），並進行功能富集分析（GO、KEGG、Cancer Hallmarks）、蛋白互作網絡分析（STRING、Cytoscape）及樞紐基因排序（Degree、MNC）。利用 Kaplan–Meier Plotter 與 UCSC Xena 評估預後影響，並在 TCGA AML 隊列中分析 TRIP13 與 FLT3、PML/RARA 及 NRAS 突變的關聯。**結果：**共鑑定 118 個 DEGs，富集於有絲分裂調控與基因組不穩定途徑。在十個樞紐基因中，僅高表現 TRIP13 與較差總生存顯著相關。TRIP13 在 NRAS 突變 AML 中表現升高，並呈現預後依賴突變背景的差異性：於 NRAS 野生型預測較差存活，於 NRAS 突變型則與較佳預後相關。**結論：**TRIP13 為具背景依賴性的 AML 預後標誌物，可優化現有風險分層，並具潛力成為治療靶點，需進一步機制驗證。

關鍵字：急性髓性白血病（AML）、TRIP13、生物資訊學、預後生物標記物

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Original Research Article

Clinical utility of human papillomavirus testing with first void urine for detecting high-grade squamous intraepithelial lesion or worse: A meta-analysis

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ABSTRACT

Background: Self-collection methods are regarded as a potential strategy to promote HPV testing for cervical cancer screening. HPV testing using urine specimens offers benefits, including its non-invasiveness. This characteristic has the potential to remove barriers associated with the procedure, such as discomfort. Nevertheless, concerns regarding the accuracy of this method persist. The present meta-analysis aims to verify the accuracy of HPV testing with first void urine (FVU). ***Materials and methods:*** A literature search was conducted in the PubMed, Embase, and Cochrane Library databases to identify studies that evaluated the performance of HPV testing with FVU. The inclusion criteria were as follows: studies that evaluated the diagnostic accuracy of HPV testing for high-grade squamous intraepithelial lesion or worse (HSIL+) with FVU. Additionally, studies that provided sufficient data for conducting a meta-analysis were assessed. The meta-analysis was conducted using the bivariate random-effects model. ***Results:*** Twenty studies with 6150 samples were identified. The meta-analysis yielded a pooled sensitivity of 84.0% (95% CI: 78.6% to 88.2%) of HPV testing with self-collected FVU for HSIL+. For specimen collection, pooled sensitivity was 88% (95% CI: 83.1% to 91.6%) in the subgroup of papers using FVU via a standardized device to evaluate HPV testing. With regard to DNA-based testing, the subgroup analysis yielded a pooled sensitivity of 86.3% (95% CI: 84% to 88.4%). ***Conclusion:*** This meta-analysis indicates that HPV testing with FVU achieves high sensitivity for detecting HSIL+. Furthermore, HPV testing employing FVU collected with a standardized device has the potential to yield marginally elevated sensitivity.

Keywords: Diagnostic Screening Programs; Human Papillomavirus DNA Tests; meta-analysis;

self-collected samples; first void urine

INTRODUCTION

A principal objective of the World Health Organization (WHO) Call to Action is to achieve a minimum participation rate of 70% among eligible women aged 35 and 45 in cervical cancer screening using high-performance tests. It is imperative to note that this initiative is being pursued with the overarching intention of eliminating cervical cancer by the year 2030[1,2]. Lack of engagement in cervical cancer screening is identified as a significant factor leading to the elevated risk of developing invasive cervical cancer observed among females not participating in such programs[2]. Among the range of cutting-edge detection systems currently available, human papillomavirus (HPV) nucleic acid amplification testing offers a robust solution that fulfils the stringent criteria for high-performance testing[3]. HPV testing has been established as a primary screening method, offering a highly sensitive approach for the detection of cervical cancer. As has been documented, HPV testing has a notably higher sensitivity for cervical precancer detection than the conventional Pap test[4]. It is noteworthy that the employment of patient self-collection strategies, such as vaginal and urine specimens for HPV testing, has been demonstrated to facilitate an augmentation in screening coverage, particularly among individuals who have not previously undergone such procedures[5,6].

Urine-based HPV testing is an alternative method of cervical screening which has been demonstrated to be promising, as it is non-invasive and has the potential to eliminate barriers such as embarrassment[7,8]. The initial portion of the urine sample is regarded as first void urine (FVU), a term which has been demonstrated to facilitate a more sensitive detection of cervical HPV. The specimen has attracted international attention as an additional non-invasive self-sampling method.[8,9]

Despite the evident benefits of HPV testing with urine specimens in expanding the scope of cervical cancer screening and the fact that its accuracy has been verified, concerns regarding the validity of FVU persist[10]. Thus, the necessity for a meta-analysis was apparent in order to evaluate the accuracy of HPV testing using FVU in cervical cancer screening.

MATERIALS AND METHODS

The present study adopts a meta-analytic approach, encompassing a rigorous synthesis of diagnostic test accuracy studies. As such, the study was reported in compliance with the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Diagnostic Test Accuracy Studies. The present study has been duly registered within the database of PROSPERO (registration number: CRD420251069764).[11]

Literature Search Strategy

A meticulous and methodical search was executed for potentially pertinent studies, applying Boolean operators within the PubMed, Embase, and Cochrane Library databases. A search was initiated in order to identify articles related to the subject. The following search terms were used: (cervical intraepithelial neoplasia or CIN2 or CIN3 or HSIL or high-grade squamous intraepithelial lesion or Uterine Cervical Dysplasia) and (Human Papillomavirus DNA Tests or HPV testing) and (urine or Urine Specimen Collection). To expand the scope of the search, both Medical Subject Headings and free texts were incorporated into the search string.

Inclusion and Exclusion Criteria

For the purpose of this study, manuscripts that evaluated the diagnostic accuracy of HPV testing for high-grade squamous intraepithelial lesion or worse (HSIL+) using first void urine specimens obtained by the study participants themselves were included. Furthermore, the present study exclusively involved those studies that employed the nucleic acid amplification test technique for HPV testing. In this meta-analysis, the population studied was comprised of individuals who participated in cervical cancer screening or were referred for colposcopy, or who were diagnosed with HSIL+. Peer-reviewed studies that adopted histopathology or colposcopy as the reference standard were deemed to have met the requisite rigor for inclusion. Studies providing sufficient diagnostic data to construct a 2x2 table on a per-sample basis were included. A broad array of article types was excluded from the selection, encompassing review articles, case reports, case series, proposals, protocols, conference abstracts, conference papers, in-house tests, and pre-prints. A final literature search was conducted on June 8, 2025, as a means of ensuring the up-to-date information was utilized in the study. An initial evaluation of the titles and abstracts was con-

ducted by one of the authors (HLL) to ascertain the potential suitability of the studies for inclusion. Following the elimination of articles deemed irrelevant, two authors (KYH and CCC) conducted a separate review of all full-text articles that met the predetermined eligibility criteria. A series of meetings were convened in order to identify and address the points of contention between the authors. The purpose of these discussions was to achieve a consensus.

Quality Assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) framework was thus employed to evaluate the methodological quality of each study included in the meta-analysis[12]. The QUADAS-2 was the basis upon which HPV testing with self-collected FVU specimens were identified as the index tests. The index tests were subsequently compared to histopathology or colposcopy results, which served as the reference standards. The authors evaluated the quality of each paper objectively. All authors took part in the assessment and resolved disagreements to reach a consensus.

Statistical Analysis

Data from each study underwent a fourfold grouping, comprising true positives, true negatives, false positives and false negatives, with the objective of conducting a data synthesis. The application of these data enabled the conduction of a diagnostic meta-analysis, the objective of which was to calculate the pooled sensitivity and specificity of HPV tests using FVU. Where the data presented in the primary text was lacking for a meta-analysis, we searched the supplementary materials of the relevant studies to collect the necessary information. The definition of the sensitivity of a diagnostic test is as follows: the proportion of individuals with the target disorder who are correctly identified as having the target disorder. Conversely, the specificity of a diagnostic test is defined as the proportion of individuals not afflicted by the target disorder who are accurately identified as not suffering from said disorder[13].

A meta-analysis was conducted using a bivariate random-effects model to produce summary estimates of sensitivity and specificity on a per sample basis. To determine the overall diagnostic value of the FVU HPV testing, its summary receiver operating characteristic curve was plotted. The presence of such a curve, located in closer proximity to the upper left corner, is an indication of superior performance[14]. To explore potential heterogeneity among the studies, a series of prespecified subgroup analyses were undertaken. These analyses were consequently conducted in accordance with the following categories: patient population, specimen collection method of FVU, technique used in the index tests, and type of reference standard. This meta-analysis yields pooled sensitivity and specificity estimates, together with corresponding 95% confidence intervals (CIs). Furthermore, a metaregression was performed using the patient population, the technique used in the index tests, and the specimen collection method of FVU as the covariates across the articles included in the study. Relative sensitivity (RS) is defined as the ratio between two estimated detection rates, specifically true positive rates, derived from different patient population (technique used the index tests or specimen collection method of FVU) in our meta-analysis[15]. All analyses were performed using RevMan version 5.4, and MetaDiSc version 2.0[16]. $p < .05$ indicated statistical significance.

RESULTS

Meta-analysis

Subsequent to the critical appraisal, a total of 20 articles were identified, with a sample size of 6,150[17-36]. The visual depiction provided in Figure 1 outlines the systematic procedure undertaken during the literature search, thereby offering insight into the process of identifying and selecting relevant studies. Table 1 offers a concise summary of the key features and attributes of the final selected articles. The studies exhibited notable variation with regard to the following aspects of their study design, the characteristics of the patient populations they encompassed, how specimens were collected, and which type of reference standard they used. One study employed a randomized controlled trial, while two were classified as pilot studies. In contrast, 17 studies enrolled participants on a prospective basis. Thirteen articles enrolled patients who underwent referral for colposcopy, and 10 studies evaluated the performance of HPV testing with FVU obtained via a standardized collection device. A thorough evaluation of the extant literature revealed that 18 manuscripts assessed the diagnostic efficacy of the index test using a DNA-based technique. Concurrently, 14 papers exclusively applied histopathology

as the reference standard. The meta-analysis yielded a pooled sensitivity of 84.0% (95% CI: 78.6% to 88.2%) and a pooled specificity of 45.2% (95% CI: 37.9% to 52.6%) of HPV testing with self-collected FVU for HSIL+ (Figure 2). Figure 3 presents the statistical data, sensitivities, and specificities of HPV testing from the included studies.

Quality of included studies

In the process of patient selection, all studies reported the random enrolment of patients and the avoidance of inappropriate exclusion criteria. Consequently, all studies were categorized as exhibiting a low risk of bias with respect to patient selection, as defined by the criteria established by the tool. The studies included in the current investigation documented that the index tests were interpreted independently of any prior knowledge of the outcomes of the reference standard tests. Consequently, all studies exhibited a low risk of bias in the context of the index tests. As demonstrated in 14 studies, the reference standard test was found to accurately identify HSIL+. In addition, 5 studies reported that the assessment of the reference standard was conducted in a blind manner with respect to the index test results. In relation to the domain of flow and timing, the findings of all studies indicated the presence of an appropriate interval between the index test and the reference standard. Furthermore, it was ascertained that all patients received a reference standard. In addition, 14 papers reported that all patients received the same reference standard. In consequence, 5 studies exhibited a low risk of bias with respect to the flow and timing domain. The patient selection, index test and reference standard of the constituent studies of the meta-analysis were found to align with the objectives of the present study within the scope of their applicability.

Subgroup analysis

The meta-analysis suggested a number of factors that may be contributing to the observed heterogeneity. Specifically, these factors encompass the patient demographic, the specimen collection method, the index tests, and the type of reference standard. Hence, subgroup analyses were employed to identify heterogeneity. For the subgroup of 13 studies that enrolled female participants who were referred to colposcopic examination and involved a total of 4966 specimens, the pooled sensitivity was identified as 85.9% (95% CI: 80.2% to 90.2%), while the pooled specificity was reported as 44.1% (95% CI: 35.4% to 53.3%). For specimen collection method, the pooled sensitivity was 88% (95% CI: 83.1% to 91.6%) and the pooled specificity was 41.3% (95% CI: 32.0% to 51.2%) in the subgroup analysis of the 10 papers that used FVU obtained via a standardized collection device to evaluate HPV testing. In terms of DNA-based testing, a pooled sensitivity of 86.3% (95% CI: 84% to 88.4%) and a pooled specificity of 42.4% (95% CI: 35.9% to 49.3%) were obtained from the subgroup analysis of the 18 papers that used DNA-based technique, and a pooled sensitivity of 44.4% (95% CI: 32.7% to 56.8%) and a pooled specificity of 68.7% (95% CI: 48.5% to 83.7%) were identified in another subgroup analysis that assessed RNA-based methodology. The results of these subgroup analyses indicated that DNA-based testing may demonstrate superior sensitivity. Moreover, this testing method, employing FVU obtained via a standardized collection device, has the potential to achieve a heightened level of sensitivity. Table 2 lists the pooled estimates from the subgroup analyses.

Metaregression

A complementary approach to investigating potential heterogeneity among the included studies is to conduct a metaregression, incorporating the following covariates: patient population, index test, and specimen collection method. The metatrgression analysis for the sensitivity of HPV testing in patients referred to colposcopy relative to those not referred to colposcopy, produced an RS of 1.1 (95% CI: 0.96 to 1.28; $p = 0.14$), which suggests that there is no significant difference between the two groups. In terms of index test, the RS of HPV testing using DNA-based methodology yielded an RS value of 1.94 (95% CI: 1.47 to 2.56; $p < 0.01$), when compared to the RNA-based testing approach. This result indicated that the DNA-based methodology may have exhibited a relatively superior sensitivity. In addition, we conducted a metaregression analysis in order to evaluate the sensitivity of HPV testing using FVU obtained via a standardized collection device against those not using the said collection device. The resulting RS was 1.15 (95% CI: 1.03 to 1.29; $p = 0.02$), providing evidence that HPV testing using FVU obtained via a standardized collection device might be significantly superior in terms of sensitivity. Table 3 presents the detailed estimates derived from metaregression analyses.

DISCUSSION

The findings of this study demonstrate that HPV testing performed using the FVU specimen achieves a high sensitivity in detecting HSIL+. To achieve the objective of 70% cervical cancer screening coverage, the WHO has strongly suggested that self-sampling specimens, including urine, be incorporated for HPV testing as an assistant approach. HPV self-sampling has gradually gained acceptance as a satisfactory method of cervical cancer screening for female patients[37]. Similarly, in an effort to assist in overcoming the barriers to achieving the objectives of the Cervical Cancer Elimination Initiative, the WHO has emphasized the development of target product profiles (TPPs) for HPV testing. The TPPs serve as a framework for the advancement and enhancement of technologies that have the potential to assist countries in achieving a minimum screening coverage of 70%. The potential application of new TPPs for HPV testing may encompass the usage of additional specimen types, such as urine[38]. This study is congruent with the objectives of the WHO, as it aims to validate the efficacy of HPV testing using FVU for the screening of cervical cancer. A parallel can be drawn to the 2024 draft of the US Preventive Services Task Force's cervical cancer screening guidelines, which now incorporates self-collection as a screening option[39]. It has been posited that the integration of urine specimens into the guideline may emerge as a viable option in light of this trend.

Subgroup and metaregression analyses indicated that DNA-based HPV testing performed with FVU and HPV testing using FVU obtained via a standardized collection device exhibited higher sensitivity for HSIL+ detection. This particular finding is consistent with the perspective previously outlined by the WHO. The WHO recommends HPV DNA testing for primary cervical cancer screening[40]. In comparing HPV DNA testing to the Pap test, it is evident that the former is more sensitive in detecting CIN2+ and allows for more extended screening intervals[41]. The findings of this study, concomitant with those of a prior meta-analysis, suggest that DNA-based urine HPV testing is a sensitive method for cervical cancer screening, contrasted by the lack of recommendation for urine RNA-based HPV testing[42]. The provision of self-collected HPV testing as a cervical cancer screening strategy to non-attendees constitutes a cost-effective solution, exhibiting a concomitant reduction in cervical cancer cases and associated mortalities. Moreover, the implementation of self-collected HPV testing enhances the level of screening participation, thereby demonstrating cost-effectiveness in comparison with the prevailing cytology-based screening methods[43-45]. In addition, the application of self-collected samples possesses the capacity to curtail healthcare expenditures and alleviate the workload of healthcare providers[46]. Colli-Pee® (a standardized collection device) has been shown to yield higher concentrations of HPV DNA compared to samples collected by the cup method, with concentrations up to 12.18 ng/μl detected in FVU[9]. Furthermore, the metaregression analysis demonstrated that HPV testing using FVU samples obtained with a standardized collection device exhibited increased sensitivity for HSIL+ cases. Therefore, it is suggested that the application of FVU in conjunction with a standardized collection device may lead to an enhancement in the sensitivity of HSIL+ detection in urine HPV testing.

The correlation between urine HPV testing and patients with LSIL, as well as women with normal Pap test results, is a noteworthy clinical concern. The positivity of high-risk HPV is 87% in FVU samples from patients with LSIL histological diagnoses. This result is comparatively lower, at 83.3%, in samples from women with normal histology[17]. Furthermore, high-risk HPV was identified in 71% of urine samples obtained from women with LSIL cytological diagnoses[47]. As reported previously, the global prevalence of HPV in females with normal cytology is approximately 10%[48]. Additionally, the global prevalence of HPV was reported to be 11.7% among women aged 50 and older[49].

The description of the advantages and disadvantages of urine HPV testing in comparison to Pap tests and cervical HPV testing requires further clarification. Self-sampling may increase coverage, accessibility, and acceptance of screening services, reducing the burden on health care providers and reducing screening costs[42,50]. Furthermore, HPV urine testing eliminates the need for a pelvic examination. This practice can result in physical and psychological discomfort for a considerable number of women undergoing Pap test and cervical HPV testing[27]. However, the sensitivity of urine HPV testing for HSIL+ is not significantly superior to that of cervical HPV testing[42].

Despite the outcomes suggesting HPV testing with FVU as a highly sensitive tool for

detecting HSIL+, and the results of meta-regression demonstrating HPV testing using FVU obtained via a standardized collection device as having elevated sensitivity, the present study is subject to the following limitations. Eight studies incorporated into the meta-analysis disclosed the cutoff value, expressed as a cycle threshold value, that would indicate a positive HPV testing result. The volume of FVU collection was documented in a mere 14 studies. A lack of consistency was observed in the volume of specimens reported from the included studies. A total of ten studies were conducted to ascertain the accuracy of urine HPV testing when utilizing a standardized specimen collection technique.

The collection of vaginal specimens for the purpose of HPV testing is an integral component of a guidelines framework for cervical cancer screening[51]. Further investigations are necessary to evaluate the accuracy of HPV testing with FVU when conducted with a standardized specimen collection process, including preanalytical handling and storage and specimen volume[52]. Furthermore, it is necessary that urine specimens for HPV testing be incorporated into cervical cancer screening guidelines. Investigations of this nature would contribute to the enhancement of the broader applicability of urine-based HPV testing.

CONCLUSIONS

The principal findings of this study demonstrate that HPV testing with FVU achieves high sensitivity for detecting HSIL+. A notable benefit of DNA-based HPV testing is its enhanced sensitivity, when compared with RNA-based testing. A potential avenue for enhancing the sensitivity of HSIL+ detection in HPV testing involves the employment of FVU in conjunction with a standardized collection device.

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TABLES

Table 1. Characteristics of studies

Table 1. Characteristics of studies

Study	Study design	Number of participants (total / data extraction)	Age	Participant population	Specimen collection	Minimal sample volume (mL)	Index test	Threshold (Ct)	High-risk HPV types detected by index test	Cervical precancer detected	Reference standard
Tranberg 2025	prospective, consecutive	(325/325)	36, 29-46 (median, IQR)	colposcopy for abnormal cytology, post-coital bleeding, women who underwent LEEP	FVU with Colli-pee®	7	Allplex HPV HR detection assay	≦ 43	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68	CIN2+	histopathology
Van Keer S 2025	prospective	(487/484)	NA	women referred to colposcopy	FVU with Colli-pee®	NA	Roche cobas® 4800	NA	HPV type 16, HPV type 18 and HPV Other (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	CIN2+	histopathology
Latsuzbaia 2025	prospective	(499/496)	NA	women referred to colposcopy	FVU with Colli-pee®	13	HarmoniaHPV	≦ 30	HPV16 and HPV18, other 12 HPV genotypes (HPV58, 33, 45, 31, 52, 35, 39, 59, 51, 56, 66, and 68)	CIN2+	histopathology, colposcopy
Van Keer 2025	prospective	(298/297)	38, 30-49 (median, IQR)	women referred to colposcopy	FVU with Colli-pee Small Volumes	10	Alinity m HR HPV assay	CN ≤ 34 for hrHPV Group A and CN ≤ 31 for hrHPV Group B.	HPV16, HPV18, HPV45, Group A (HPV31/33/52/58), and Group B (HPV35/39/51/56/59/66/68)	CIN2+	histopathology, colposcopy
Giubbi 2024	prospective	(490/471)	37, 31-47 (median, IQR)	women referred to colposcopy	FVU with Colli-Pee FV5000	13	OncoPredict HPV SCR assay	Ct ≤ 44	HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68	CIN2+	histopathology
Latsuzbaia 2024	prospective	(490/450)	37, 31-47 (median, IQR)	women referred to colposcopy	FVU with Colli-Pee FV5000	NA	OncoPredict HPV QT assay	NA	QT1: HPV 16/18/45; QT2: HPV 31/33/52; QT3: HPV 35/58/59; QT4: HPV 39/51/56	CIN2+	histopathology
Davies 2024	randomized controlled trial	(480/446)	32 (median)	Colposcopy attendees with abnormal cervical screening	FVU with Colli-pee® or standard-pot-collected urine	6.6	Roche cobas® 8800		HPV type 16, HPV type 18 and HPV Other (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	CIN2+	histopathology, colposcopy
Zhao 2023	prospective	(732/732)	41.2 ± 11.1 (mean)	indications for colposcopy due to abnormal cervical cytology or infection with HPV16 and 18	FVU	10	ABI7500 real-time PCR system		HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology

Study	Study design	Number of participants (total / data extraction)	Age	Participant population	Specimen collection	Minimal sample volume (mL)	Index test	Threshold (Ct)	High-risk HPV types detected by index test	Cervical precancer detected	Reference standard
Latsuzbaia 2023	prospective	(492/492)	NA	women referred to colposcopy	FVU with Colli-pee®	13	Alinity m System	HPV 16: ≦32	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology, colposcopy
Van Keer 2022	prospective	(492/492)	40, 31-50 (median, IQR)	women referred to colposcopy	FVU with Colli-pee®	13	BD Onclarity HPV Assay	≦34.2, (HPV 16:≦38.3)	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology, colposcopy
Punyashthira 2022	prospective	(96/96)	47.5 (mean)	colposcopy for abnormal cytology	FVU	10-15	Anyplex II HPV testing	NA	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology
Van Keer 2021	prospective	(493/493)	40, 19-72 (median, range)	women referred to colposcopy	FVU with Colli-pee®	13	Abbott m2000 System	≦32	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology, colposcopy
Padhy 2020	prospective	(189/113)	41(median)	cervical cancer screening	FVU	NA	Aptima HPV assay	NA	mRNA for HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology
Rohner 2020	prospective	(307/307)	36, 31-45 (median, IQR)	women referred to a colposcopy, cervical cancer screening	FVU	20	BD Onclarity HPV Assay	≦34.2, (HPV 16:≦38.3)	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology
Asciutto 2018	prospective	(209/164)	30, 20-68 (median, range)	women referred to a colposcopy	FVU	NA	Aptima HPV assay	NA	mRNA for HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	CIN2+	histopathology
Asciutto 2017	prospective	(218/199)	35.2 ± 10.8 (mean)	women with an abnormal cervical smear in the screening program or with symptoms	FVU	NA	Roche cobas® 4800	NA	HPV type 16, HPV type 18 and HPV Other (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	CIN2+	histopathology
Khunamornpong 2016	prospective	(168/123)	45.8 ± 8.1 (mean)	women who had previous positiveHPVtest or with previous cervical epithelial lesions	FVU	5-50	Roche cobas® 4800	NA	HPV type 16, HPV type 18 and HPV Other (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	CIN2+	histopathology
Senkomago 2016	pilot study	(37/37)	42, 30-63 (median, range)	women with abnormal cytology or persistent HPV	FVU	20	Trovagene	NA	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	CIN2+	histopathology

Study	Study design	Number of participants (total / data extraction)	Age	Participant population	Specimen collection	Minimal sample volume (mL)	Index test	Threshold (Ct)	High-risk HPV types detected by index test	Cervical precancer detected	Reference standard
				infection or treat-ment by loop electrical excision procedure							
Bernal 2014	prospective	(125/80)	35.5, 21-65 (median, range)	women abnormal Pap smear screening results	FVU	≧20	Roche cobas® 4800	NA	HPV type 16, HPV type 18 and HPV Other (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)	CIN2+	histopathology
Sahasrabuddhe 2014	pilot study	(72/71)	28, 24-34 (median, range)	women referred to colposcopy for abnormal cervical cancer screening results	FVU	NA	Trovagene	NA	HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 68, 70	CIN2+	histopathology

CIN2+: cervical intraepithelial neoplasia 2 or worse; CT: cycle threshold; FVU: first-void urine; HPV: human papillomavirus; IQR: interquartile range; NA: not available; LEEP: loop electrosurgical excision procedure

Table 2. Subgroup analyses of the diagnostic accuracy of HPV testing using first void urine

Subgroup	Number of studies	Number of samples	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Patient population				
Women referred to colposcopy	13	4966	85.9 (80.2%-90.2%)	44.1 (35.4%-53.3%)
Specimen collection				
FVU	10	1922	76.7 (67.9%-83.6%)	49.1 (38.8%-59.5%)
FVU with Colli-pee	10	4228	88 (83.1%-91.6%)	41.3 (32.0%-51.2%)
Index test				
DNA-based testing	18	5873	86.3% (84%-88.4%)	42.4% (35.9%-49.3%)
RNA-based testing	2	277	44.4% (32.7%-56.8%)	68.7% (48.5%-83.7%)
Reference standard				
histopathology	14	3652	81.7% (73.4%-87.9%)	46.5% (36.9%-56.4%)
histopathology or colposcopy	6	2498	88% (85%-90.4%)	42.1% (33.7%-51%)

CI: confidence interval, FVU: first void urine, HPV: human papillomavirus

Table 3. Estimates of meta-regression

covariate	Estimate			
	Relative sensitivity (95% CI)	*p*-value	Relative specificity (95% CI)	*p*-value
women referred to colposcopy vs not	1.1 (0.96-1.28)	0.14	0.94 (0.67-1.32)	0.72
DNA-based testing vs RNA-based testing	1.94 (1.47-2.56)	<0.01	0.61 (0.45-0.84)	0.02
FVU with Colli-pee vs not	1.15 (1.03-1.29)	0.02	0.84 (0.61-1.15)	0.29

CI: confidence interval, FVU: first void urine

FIGURE AND FIGURE LEGENDS

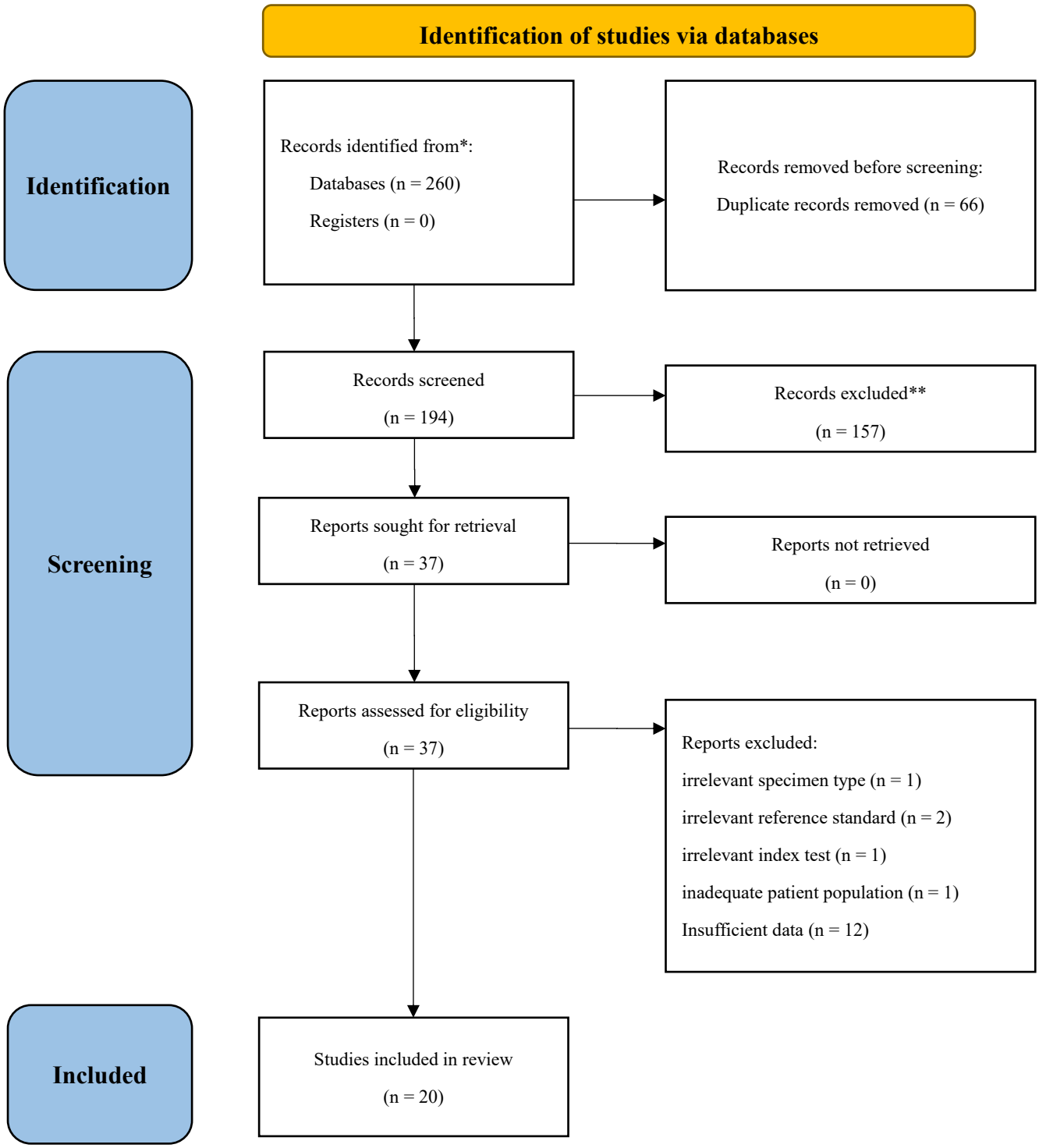

Figure 1. Flow diagram of literature search

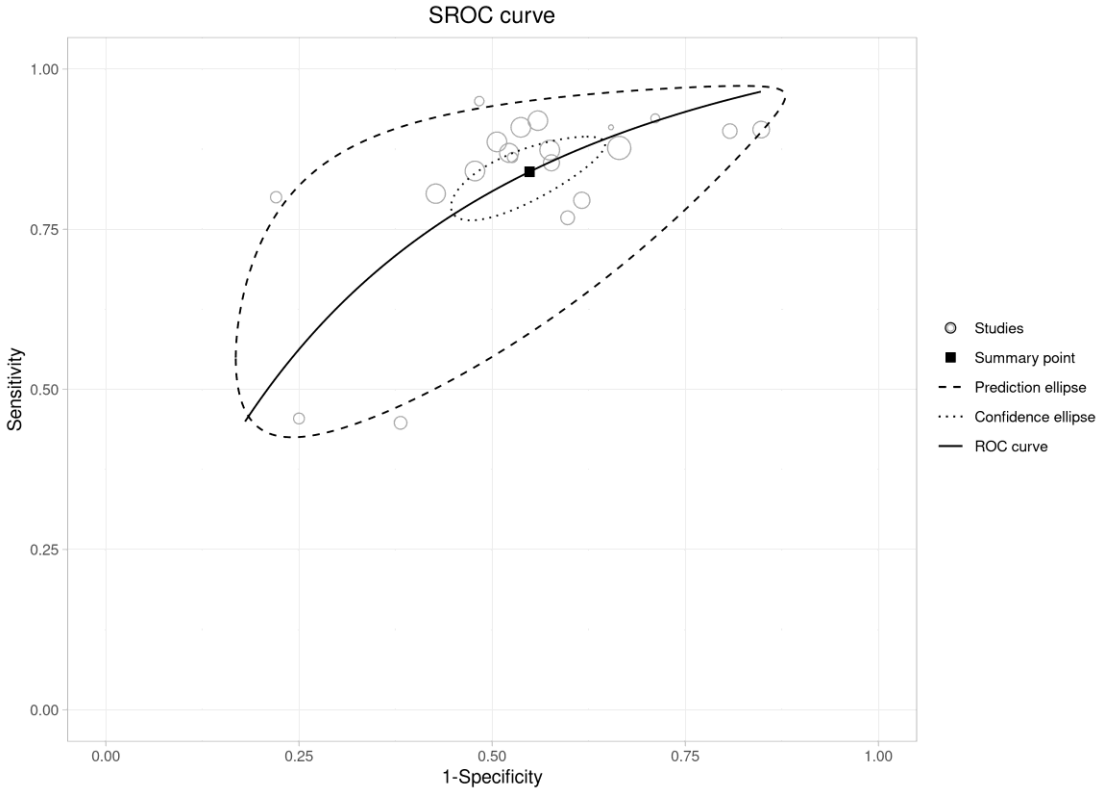

Figure 2. Summary estimate of the SROC curve indicates a pooled sensitivity of 84.0% (95% CI: 78.6% to 88.2%) and a pooled specificity of 45.2% (95% CI: 37.9% to 52.6%) for HPV testing.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Asciutto 2017	86	52	26	35	0.77 [0.68, 0.84]	0.40 [0.30, 0.51]
Asciutto 2018	30	37	37	60	0.45 [0.33, 0.57]	0.62 [0.51, 0.72]
Bernal 2014	19	29	1	31	0.95 [0.75, 1.00]	0.52 [0.38, 0.65]
Davies 2024	112	84	12	20	0.90 [0.84, 0.95]	0.19 [0.12, 0.28]
Giubbi 2024	87	155	21	208	0.81 [0.72, 0.88]	0.57 [0.52, 0.62]
Khunamornpong 2016	4	26	1	92	0.80 [0.28, 0.99]	0.78 [0.69, 0.85]
Latsuzbaia 2023	74	193	14	211	0.84 [0.75, 0.91]	0.52 [0.47, 0.57]
Latsuzbaia 2024	93	179	14	164	0.87 [0.79, 0.93]	0.48 [0.42, 0.53]
Latsuzbaia 2025	76	235	11	174	0.87 [0.79, 0.94]	0.43 [0.38, 0.47]
Padhy 2020	15	20	18	60	0.45 [0.28, 0.64]	0.75 [0.64, 0.84]
Punyashthira 2022	50	20	8	18	0.86 [0.75, 0.94]	0.47 [0.31, 0.64]
Rohner 2020	66	138	17	86	0.80 [0.69, 0.88]	0.38 [0.32, 0.45]
Sahasrabuddhe 2014	24	32	2	13	0.92 [0.75, 0.99]	0.29 [0.16, 0.44]
Senkomago 2016	10	17	1	9	0.91 [0.59, 1.00]	0.35 [0.17, 0.56]
Tranberg 2025	163	123	17	22	0.91 [0.85, 0.94]	0.15 [0.10, 0.22]
Van Keer 2021	78	205	10	200	0.89 [0.80, 0.94]	0.49 [0.44, 0.54]
Van Keer 2022	80	217	8	187	0.91 [0.83, 0.96]	0.46 [0.41, 0.51]
Van Keer 2025	70	124	12	91	0.85 [0.76, 0.92]	0.42 [0.36, 0.49]
Van Keer S 2025	80	222	7	175	0.92 [0.84, 0.97]	0.44 [0.39, 0.49]
Zhao 2023	114	400	16	202	0.88 [0.81, 0.93]	0.34 [0.30, 0.37]

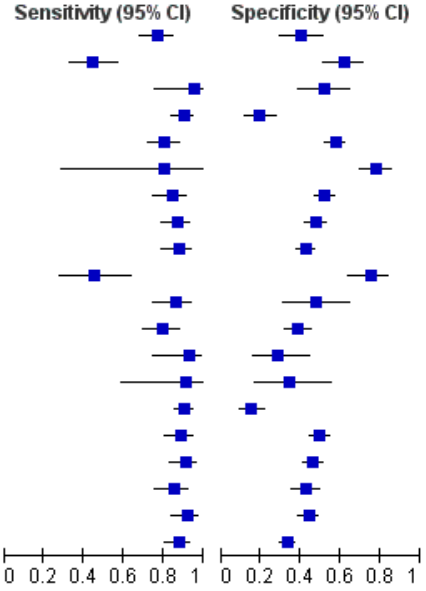

Figure 3. Forest plots showing the sensitivity and specificity with 95% CIs of HPV tests of the included studies (CI: confidence interval, FN: false negative, FP: false positive, TN: true negative, TP: true positive).

Clinical utility of human papillomavirus testing with first void urine for detecting high-grade squamous intraepithelial lesion or worse: A meta-analysis

人類乳突病毒檢測使用前段排出尿液執行子宮頸癌篩檢的準確度：統合分析

蕭可妤[1]　林秀玲[2]　陳正杰[3,*]

中文摘要

背景：世界衛生組織（WHO）提出的一個目標，讓 70%符合資格的婦女在 35 歲與 45 歲間，使用高效能的檢測方法接受子宮頸癌篩檢，以期在 2030 年前消除子宮頸癌。人類乳突病毒檢測(HPV testing) 的敏感度比抹片高，WHO 推薦為第一線篩檢工具。況且提供自我採檢樣本更可以提高婦女接受子宮頸癌篩檢的比例。我國於 2025 年起，將 HPV testing 納入健保給付，目的為增加篩檢率與迎合 WHO 在 2030 年前清除子宮頸癌的目標。前段排出尿液檢體(first void urine, FVU)可用於 HPV testing，但準確性正探討中。FVU 含較高濃度的 HPV DNA，推測可使用 FVU 提高篩檢敏感度。因此本研究目的為驗證 HPV testing 伴隨 FVU 篩檢子宮頸癌的準確性。**材料與方法**：於 PubMed，Embase 與 Cochrane library 資料庫中，以(cervical intraepithelial neoplasia or CIN2 or CIN3 or HSIL or high-grade squamous intraepithelial lesion or Uterine Cervical Dysplasia) and (Human Papillomavirus DNA Tests or HPV testing) and (urine or Urine Specimen Collection)關鍵字搜尋。納入條件為：研究 FVU 偵測高度子宮頸癌前期及更嚴重病灶(high-grade squamous intraepithelial lesion or worse, HSIL+)的文獻；以 histopathology 或 colposcopy 為黃金標準之文獻。統合分析的分法以 random-effects model。**結果**：共納入 20 篇文章，樣本數為 6150。統合分析結果顯示，HPV testing 使用 FVU 偵測 HSIL+ 的 pooled sensitivity 為 84.0% (95% CI: 78.6% to 88.2%)，pooled specificity 為 45.2% (95% CI: 37.9% to 52.6%)。子族群分析指出，使用標準化容器採集 FVU，HPV testing 的 pooled sensitivity 為 88% (95% CI: 83.1%至 91.6%)。**結論**：HPV testing 伴隨 FVU 篩檢子宮頸癌具有高敏感度。HPV testing 使用標準化容器採集的 FVU 樣本，可略為提升敏感度。

關鍵字：篩檢計畫、人類乳突病毒檢測、統合分析、自我採集檢體、前段排出尿液檢體

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A Pilot Study on the Implementation and Preliminary Outcomes of a Hospital at Home Program in a Regional Hospital
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Review Article

A Pilot Study on the Implementation and Preliminary Outcomes of a Hospital at Home Program in a Regional Hospital

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ABSTRACT

Background: With the global trend of population aging and increasing chronic diseases, there is a growing emphasis on Hospital at Home (HaH) models to alleviate the burden on healthcare systems and improve care efficiency. This study aims to explore the preliminary implementation and outcomes of acute care at home in a regional hospital in northern Taiwan. ***Objective:*** To analyze the sources of enrollment, indications, treatment outcomes, and post-discharge follow-up of patients enrolled in the acute home care program from July 2024 to March 2025, and to evaluate the feasibility and effectiveness of home-based acute care as an alternative to hospitalization. ***Methods*** This retrospective study collected data from 17 patients who met the criteria for acute home care enrollment. Patient demographics, care processes, treatment outcomes, and emergency department visits or hospitalizations within 3 and 14 days post-discharge were analyzed. ***Results:*** A total of 17 patients (7 males and 10 females) were enrolled, with a mean age of 78.2 ± 9.2 years. The majority of patients (52.9%) were residents of care facilities. The most common indication for enrollment was urinary tract infection (88.2%). Among all cases, 88.2% achieved clinical resolution and were referred back to their original medical teams. No patients required emergency visits or hospitalization within 3 or 14 days after discharge, aligning with the national health insurance data. One case (6.67%) exceeded the target treatment duration due to the need for extended antibiotic therapy for soft tissue infection. ***Conclusion:*** The results suggest that acute home care can effectively control infections without increasing the risk of

emergency department visits or hospitalization. Successful implementation requires stable patient vital signs, clear treatment plans, flexible clinical decision-making, and comprehensive support for patients and families. Home-based acute care could serve as a viable alternative to traditional inpatient care.

Keywords: Hospital at Home, home-based medical care integration program, Antibiotic Therapy

INTRODUCTION

With the global trend of population aging and increase of patients with chronic diseases, the pressure on healthcare systems is rising and there is a growing emphasis on Hospital at Home (HaH) models to alleviate the burden on healthcare systems and improve care efficiency, which has become an important link between home-based medical care and acute healthcare systems. HaH means when a patient suffers from an acute infection, which is pneumonia, urinary tract infection or soft tissue infection and only needs antibiotic treatment according to physician evaluation, the patient may accept the hospitalization services in situ including timely evaluation, preliminary treatment and medical referral if necessary[1,2].

The National Health Insurance Administration of Ministry of Health And Welfare (hereinafter referred to as NHIA) announced the Pilot Hospital at Home Program Covered by National Health Insurance (hereinafter referred to as the Pilot Program) should be implemented upon July 1st, 2024 on May 24th, 2024 with the aim of providing appropriate home-based medical cares to specific acute patients as an alternative service to hospitalization, improving the quality of home-based care for the acute patients and reducing the hospital visits of patients who live in the care facilities due to acute problems[3].

The Hospital-at-Home (HaH) model is a healthcare delivery approach that provides hospital-level, acute care services to patients in their homes rather than in a traditional inpatient setting. While HaH programs vary internationally, they often incorporate a combination of in-person medical visits and remote monitoring technologies, depending on patient condition and local medical infrastructure. In the context of this study, the HaH model implemented is primarily in-person home-based care, delivered by a multidisciplinary team including physicians, nurses, and allied health professionals.

Although some international HaH models are heavily reliant on telehealth and remote monitoring systems[4], the version launched under Taiwan's National Health Insurance emphasizes face-to-face care at the patient's residence, with remote consultation used primarily for initial assessment and follow-up support when appropriate. This approach was selected to better accommodate elderly and functionally impaired patients who may have difficulty using telecommunication devices independently.

As indicated by WHO, the advancements of telemedicine and smart health monitoring technologies have led to a rapid evolution of the home-based medical care model[5]. According to the statistics of the Health Promotion Administration of Ministry of Health and Welfare, Taiwan, over 60% of the elderly suffer from multiple chronic diseases, and the worsening of part of the acute problems consequential can be prevented via appropriate home-based treatments. Some studies have revealed, HaH can reduce unnecessary emergency department visits[6]. Although the purpose of hospitalization is disease treatment, for some patients especially the weak or elderly, HaH can not only reduce the risk of cross infection in hospital, but also alleviate the burden of the patients. The model of HaH allows the patients to accept medical cares in familiar environments and decreases their readmission rate[7,8]. Therefore, it can not only alleviate the burden of healthcare systems, but also enhance the autonomy and safety of the patients and enable them to receive timely and proper cares to improve the ability of the patients and their carers to cope with acute problems at home[9].

In this study, we performed a preliminary analysis of diagnosis, enrollment, treatment duration, and emergency department visits or hospitalizations occurring within 3 and 14 days after the cases of patients enrolled in our hospital's acute home care (HaH) program were closed. We also presented the outcomes of the program, along with the experiences and limitations encountered during its practical implementation, from the perspective of home-based care professionals. This was done with the expectation that HaH will better meet the needs of the public.

MATERIALS AND METHODS

This home care facility is affiliated with a regional public hospital in Northern Taiwan. It is currently staffed with four home care nurses who provide catheter management and nursing guidance. In line with national health policies, the facility also participates in the pilot Hospital-at-Home (HaH) program.

I. This study is designed to collect data from patients in a district hospital in Taipei City who meet the eligibility criteria for the Hospital-at-Home pilot program.

II. The data collection instrument was the application form used for patient enrollment in the National Health Insurance Hospital-at-Home pilot program.

III. A total of 17 HaH cases enrolled at the home care facility between July 2024 and March 2025 were included in this study.

IV. Data were analyzed using IBM SPSS Statistics version 25.0. Continuous variables are presented as mean ± standard deviation, and categorical variables are expressed as frequency (percentage). This preliminary analysis aimed to explore patients' diagnoses, enrollment models, duration of care, and whether they visited the emergency department or were hospitalized within 3 and 14 days after case closure.

Interventions

I. Home-based Medical Care Integration Program Covered by National Health Insurance

It's been more than 20 years since the publication of National Health Insurance Fee Schedule and Reference List for Medical Services of Taiwan in 1995[10], but the service item that a physician may prescribe and prepare medications in the residence of a patient hasn't been included. Our hospital has been firstly engaged in the Home-based Medical Care Integration Program covered by National Health Insurance since March 2016 and has been providing the home-based medical visits to the patients who needed medical attentions explicitly but were difficult to go out due to disability or illness. The patients who met the enrollment criteria were further classified into three caring stages including "Home-based Care Stage", "Severe Home-based Care Stage" and "Palliative Care Stage"[11] based on severity of their diseases.

After the patients were enrolled, the home-based nurses explained the Home-based Medical Care Integration Program to families of the patients. If the families agreed to accept relevant services, they would sign the letters of consent. The advantage of the home-based medical cares provided by our hospital lies in the care transition among the three stages mentioned above, which is arranged for keeping service continuity and resolving the dilemma that a home-based care case must be closed when the tracheal tube of the patient involved is removed in accordance with previous regulations as the severe home-based care stage may be converted into the home-based care stage with original caring team. If a case requires cross-functional cares, the following services may be provided: home visits made by pharmacists to provide medication integration, medication guidance and medication consultation and even to deliver prescriptions to door for the elderly, comprehensive nutritional assessments, diagnoses and interventions made by nutritionists based on diseases and nutritional and dietary needs of the patients as well as the caring capability of their families to improve the patients' nutritional statuses, blood collection and test at home made by laboratory technicians for patients with mobility impairment and appropriate rehabilitation advices and exercise prescriptions offered by physical therapists and occupational therapists to the patients during home visits in order to mitigate decline and disability of physical function of the patients.

II. Pilot HaH Program Covered by National Health Insurance

The patients enrolled in our study were those who were supposed to be hospitalized but suitable for accepting home-based medical care due to pneumonia, urinary tract infection or soft tissue infection according to the diagnoses of their attending physicians and met one of the following criteria:

1. Patients enrolled in the Home-based Medical Care Integration Program, home-based care stage of the Prospective Integrated Payment Program for Patients with Respirator Dependence Covered by National Health Insurance or Integrated Care Program for Post-acute Stage Covered by National Health Insurance with home-based medical care and disability (Barthel score < 60) and those enrolled in the Home-based Care Stage or Palliative Care Stage (hereinafter referred to as patients at home).

2. Patients who live in the care facilities, participate in the "Program for Reducing Medical Institution Visits of Patients Living in Residential Care institutions" and may accept general outpatient services in the care facilities after obtaining consent of the insurer pursuant to Article 21 of Regulations Governing the Application of Specific Medical Technique and Medical Device. 3. Emergency Patients: those who

are difficult to go out for medical attention due to disability (Barthel score < 60) or disease.

A case should be closed if the patient during enrollment meets one of the following conditions: death, relocation, refusal to visit, completion of treatment or alleviation of disease, no need for continuous HaH, referral to emergency department or hospitalization and being enrolled in another hospital. In addition, NHIA also has established some observation indexes for the cases closed to provide references for decision on whether to implement relevant programs in the next year: 1. Rate of referral to emergency department in 3 days after case closure; 2. Rate of referral to emergency department in 14 days after case closure; 3. Rate of referral to hospitalization in 3 days after case closure and 4. Rate of referral to hospitalization in 14 days after case closure.

RESULT

Taipei City Hospital set up a HaH Co-care Group in July 2024 and filed the Pilot HaH Program and obtained the approval of NHIA of Ministry of Health And Welfare to implement the program. If a patient visited by a physician and home-based nurse met the clinical indications for case enrollment in the pilot program, specimen collection and testing (blood routine, urine routine and urine culture etc.) would be carried out for enrollment evaluation after the family of the patient was well informed and agreed. After the testing reports were issued, the group members would conduct an enrollment evaluation and reach a consensus on use of antibiotics. The enrollment procedure for HaH program in our hospital is as shown in Figure 1.

Total 17 patients met the enrollment criteria of NHIA based on their specimen testing results from July 2024 to March 2025 including 7 males (41.2%) and 10 females (59.8%) with a mean age of 78.2 years. The patients with Disability Cards made up 47.1%, those whose carers were employees of the care facilities accounted for 52.9%, those with decreased consciousness were 52.9%, those who were fed with nasogastric tubes made up 88.2%, those who used urethral catheters for urination accounted for 88.2% and those who were classified into Completely Dependent in ADLs made up 94.1% (Table 1).

As indicated in the enrollment evaluation, the main source of patients enrolled was 9 residents (52.9%) of care facilities, the most common indication for enrollment was urinary tract infection (88.2%) and the acute home care model mainly was treatment in the care facilities (52.9%) (Table 2).

The evaluation on the cases closed suggested, patients not requiring a long-term care accounted for 76.4%. As for information of cases closed, 88.2% of the patients contacted their original medical teams after their diseases were alleviated or cured (Table 3). Our further analysis demonstrated, the data of the patients who were not sent to the emergency department or were not hospitalized as their infections were controlled in 3 to 14 days after case closure is consistent with the statistics provided by NHIA[12]. In addition, the proportion of the case where the actual treatment duration exceeded the target treatment duration was 6.67% (Table 4) based on our calculation. In this case, the patient was suffered from soft tissue infection and the target treatment duration was 6 days. However, the antibiotic administration duration was adjusted to 7 days according to physician evaluation as the patient had a fever with widespread infection. When an acute patient is treated at home, the home-based medical nurses will assume more responsibilities and take more risks of potential disease change. Furthermore, the antibiotic administration must not be stopped until there is a clear treatment effect and the vital signs are stable clinically.

DISCUSSION

This pilot study demonstrated the feasibility and preliminary outcomes of implementing the Hospital at Home (HaH) model in a regional hospital in Taiwan. The findings revealed that 88.2% of patients successfully completed infection treatment at home without requiring emergency department visits or rehospitalization within 3 or 14 days. These results indicate that the HaH model is both safe and effective for managing acute infections in clinically stable patients. Only one patient required extended treatment due to soft tissue infection, suggesting that most patients could complete care within the planned period.

The study population was predominantly elderly, with a mean age of 78.2 years, and exhibited high dependency, as 94.1% required full assistance with activities of daily living (ADLs) and 88.2% relied on nasogastric or urinary catheters. For this vulnerable group, HaH offers significant benefits by reducing the risk of hospital-acquired infections and preserving home environment stability, which is critical for maintaining functional status and psychological well-being.[13]. This aligns with prior studies highlighting HaH as a new solution for acute care in super-aged societies, alleviating hospital

overcrowding while improving patient quality of life[14].

Additionally, the absence of emergency visits or readmissions within 14 days post-treatment aligns with Taiwan's national health performance indicators. This suggests that HaH may alleviate the burden on hospital resources by diverting non-critical patients from emergency departments and inpatient wards[15.16]. The outcomes observed in this study are consistent with the objectives of Taiwan's National Health Insurance HaH pilot program, launched in July 2024, which provides bundled payment for pneumonia, urinary tract infections, and soft tissue infections, while incorporating remote patient monitoring to ensure safety[17].

Despite these promising results, several challenges were identified. These include limited medical staffing, insufficient emergency equipment for home use, and reduced capacity for care during nights and holidays. Similar barriers have been reported in both Taiwanese and international HaH programs. In particular, the role of nurse practitioners has been emphasized as critical for patient screening, transitional care, home visits, and urgent interventions, highlighting the importance of interprofessional collaboration for the sustainable scaling of HaH[18].

To overcome these barriers, investment in medical support infrastructure and the development of supportive policies are essential for ensuring the safety, sustainability, and scalability of HaH programs.[19]

Recommendations

Based on the study findings and existing literature, the following recommendations are proposed to enhance the effectiveness and sustainability of HaH programs:

1. Strengthen Medical Infrastructure: Provision of portable emergency equipment and training for healthcare staff to improve care capacity during off-hours.
2. Implement Telehealth Solutions: Utilize remote monitoring and telemedicine technologies to support clinical decision-making and timely interventions.
3. Policy and Reimbursement Alignment: Develop and adjust health policies and reimbursement frameworks to incentivize HaH adoption and ensure financial sustainability.
4. Focus on High-Risk Populations: Prioritize HaH services for elderly, disabled, and multi-morbid patients who benefit most from home-based acute care.
5. Continuous Outcome Monitoring: Establish systematic evaluation aligned with national health indicators to assess safety, efficacy, and patient satisfaction over time.

CONCLUSION

The Hospital at Home program shows substantial potential to improve patient outcomes, reduce healthcare system burdens, and maintain quality of life among elderly patients with complex healthcare needs. With adequate resource allocation, technological integration, and policy support, HaH can be a valuable component of the healthcare delivery system.

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TABLES

Table 1. Basic Data and Physical Conditions of the Patients (N=17)

		Male		Female		Sum	
		N	%	N	%	N	%
Gender		7	41.2%	10	59.8%	17	100.0%
Age	M±SD	73.1±9.3		81.5±8.1		78.2±9.2	
Status							
	Ordinary	0	0.0%	3	17.6%	3	17.6%
	Patient with medium or low income	2	11.8%	0	0.0%	2	11.8%
	Patient with low income	3	17.6%	0	0.0%	3	17.6%
	Patient with Disability Card	2	11.8%	6	35.3%	8	47.1%
	Veteran	0	0.0%	1	5.9%	1	5.9%
Carer							
	Patients' Children	0	0.0%	3	17.6%	3	17.6%
	Foreign Nursing Workers	0	0.0%	4	23.5%	4	23.5%
	Patients' Spouses	1	5.9%	0	0.0%	1	5.9%
	Employees of Care Facilities	6	35.3%	3	17.6%	9	52.9%
Consciousness State							
	Conscious	2	11.8%	2	11.8%	4	23.5%
	Confused	3	17.6%	1	5.9%	4	23.5%
	Dull	2	11.8%	7	41.2%	9	52.9%
Food Intake							
	Food intake via mouth	1	5.9%	1	5.9%	2	11.8%
	Nasogastric feeding	6	35.3%	9	52.9%	15	88.2%
Excretion							
	Incontinence of urine and feces	0	0.0%	2	11.8%	2	11.8%
	Urethral catheter	7	41.2%	8	47.1%	15	88.2%
Activity of Daily Living Scale							
	Completely Dependent	7	41.2%	9	52.9%	16	94.1%
	Severely Dependent	0	0.0%	1	5.9%	1	5.9%
	Moderately Dependent	0	0.0%	0	0.0%	0	0.0%
	Mildly Dependent	0	0.0%	0	0.0%	0	0.0%
	Completely Independent	0	0.0%	0	0.0%	0	0.0%

The data is presented as numbers (percentages)

Table 2. Enrollment Evaluation (N = 17)

	Male		Female		Sum	
	N	%	N	%	N	%
Enrollment Source						
Home-based Medical Care Integration Program	1	5.9%	6	35.3%	7	41.2%
Residential Care Facilities	6	35.3%	3	17.6%	9	52.9%
Emergency Department of Hospital	0	0.0%	1	5.9%	1	5.9%
Enrollment Indication						
Pneumonia	0	0.0%	0	0.0%	0	0.0%
Infection of urinary tract	7	41.2%	8	47.1%	15	88.2%
Soft Tissue Infection	0	0.0%	2	11.8%	2	11.8%
Acute Home Medical Care Model						
Treatment at Home	1	5.9%	6	35.3%	7	41.2%
Treatment in Care Facilities	6	35.3%	3	17.6%	9	52.9%
Returning Home for Treatment from Emergency Department	0	0.0%	1	5.9%	1	5.9%

Table 3. Evaluation on Cases Closed (N = 17)

	Male		Female		Sum	
	N	%	N	%	N	%
Need for Long-term Care						
Patients Requiring Long-term Care	1	5.9%	3	17.6%	4	23.5%
Patients Cared by Foreign Nursing Workers	0	0.0%	4	23.5%	4	23.5%
Patients in Care Facilities	6	35.3%	3	17.6%	9	52.9%
Cases where treatment durations are consistent with the target durations[1]						
Infection of urinary tract	7	100.0%	6	100.0%		
Soft Tissue Infection	0	0.0%	1	50.0%		
Information of Cases Closed						
Contacting the original medical care team after disease is alleviated or cured	7	41.2%	8	47.1%	15	88.2%
Referral to Emergency Department/ Hospitalization	0	0.0%	1	5.9%	1	5.9%
Death	0	0.0%	1	5.9%	1	5.9%

The data is presented as numbers (percentages)

Note 1. Targets and upper limits of treatment durations of the diseases:

Indication	Formulated on May 24th, 2024		Formulated on February 3rd, 2025	
	Target	Upper Limit	Target	Upper Limit
Pneumonia	9	14	10	14
Infection of urinary tract	7	9	7	9
Soft Tissue Infection	6	8	7	9

Table 4. Monitoring on Observation Indexes (N = 17)

	Male		Female		Sum	
	N	%	N	%	N	%
Rate of referral to emergency department						
3 Days[1]	0	0.0%	0	0.0%	0	0.0%
14 Days[2]	0	0.0%	0	0.0%	0	0.0%
Rate of referral to hospitalization						
3 Days[3]	0	0.0%	0	0.0%	0	0.0%
14 Days[4]	0	0.0%	0	0.0%	0	0.0%
Rate of alleviation or cure[5]					15	88.2%
Rate of case where treatment duration exceeded the target duration[6]					1	6.67%

The data is presented as numbers (percentages)

FIGURE AND FIGURE LEGEND

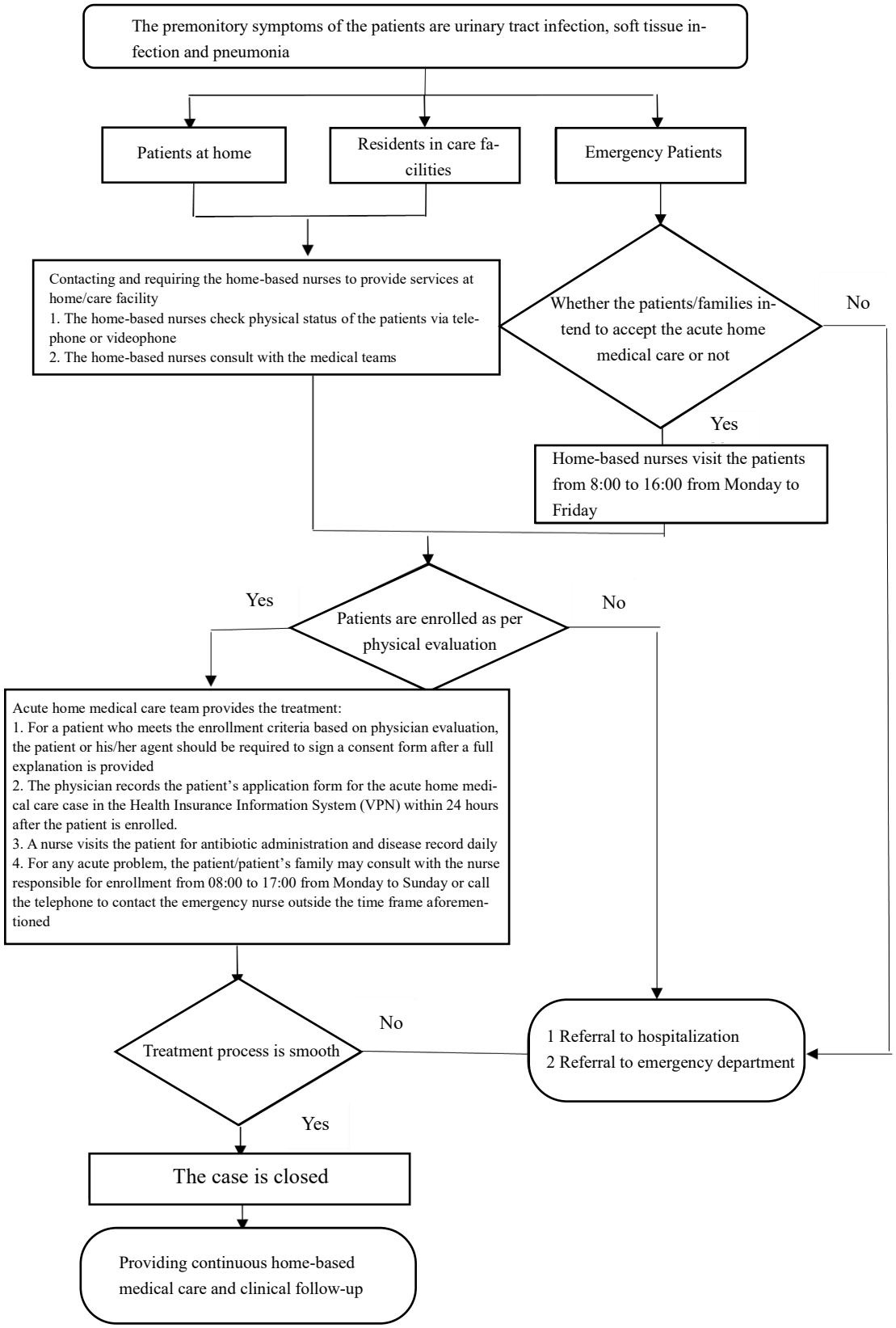

Figure 1. Enrollment Procedure for HaH Program

A Pilot Study on the Implementation and Preliminary Outcomes of a Hospital at Home Program in a Regional Hospital

在宅急症照護於區域醫院之試辦經驗與初步成效分析

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中文摘要

研究目的：本研究旨在分析某區域醫院在宅急症照護推動之分析。**材料與方法：**本文為回溯性研究，收集北部某區域醫院 2024 年 7 月至 2025 年 3 月符合在宅急症照護收案之病人為對象，分析其過程及結果。**結果：**共收案 17 位病人，男性 7 位，女性 10 位，平均年齡為 78.2±9.2 歲，病人收案來源以照護機構住民最多為 52.9%，收案適應症以尿路感染最多達 88.2%，結案資訊緩解完治聯繫原醫療團隊佔 88.2%。進一步探討個案於結案後 3 天及 14 天因感染獲得控制未有轉急診或住院情況與健保署統計資料相符，另計算有超出計畫目標天數案件比率為 6.67%，此為軟組織感染個案原治療目標為 6 天收案過程因發燒且感染範圍較大經醫師評估調整抗生素施打為 7 天，在本研究中，儘管有少數個案超過計畫目標天數，但整體結果顯示在宅急症照護能有效控制病情，且病人在照護過程中未出現需要轉急診或住院的情況，這一結果與健保署的統計資料相符，證實居家醫療照護可以成為傳統住院治療的一種有效替代方案。然而，居家醫療照護的成功實施依賴於病人生命徵象穩定且治療方案明確。在某些情況下，病人可能需要調整抗生素治療計劃，並延長治療時間，這需要醫療團隊在進行臨床決策時保持靈活性。但在推行過程中仍需關注病情變化風險的管理、治療方案的靈活調整，及對病人及家屬的全方位支持，以確保治療效果及病人的生活品質。

關鍵字：在宅急症照護、居家醫療照護整合計畫、抗生素

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Review Article

Resistance to thyroid hormone: A case report and the literatures review

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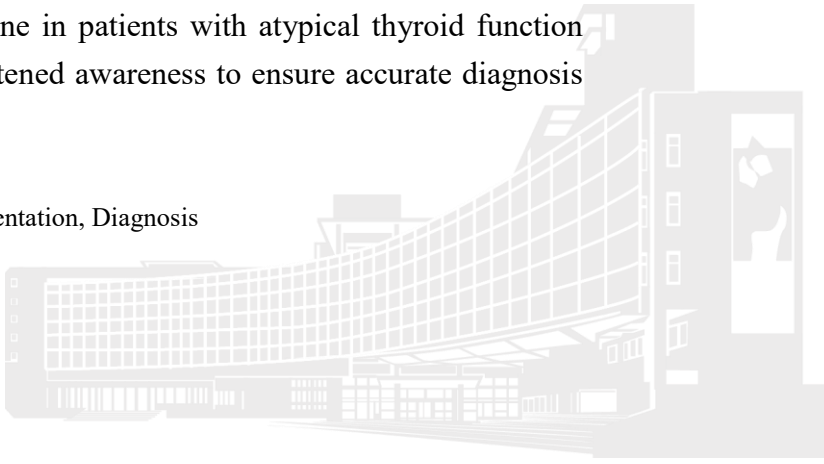
ABSTRACT

Resistance to thyroid hormone is a rare genetic disorder characterized by reduced tissue responsiveness to thyroid hormones due to mutations in thyroid hormone receptor genes. This condition leads to elevated serum free triiodothyronine and thyroxine levels with normal or mildly elevated thyroid-stimulating hormone levels. Clinically, patients may exhibit symptoms of both thyroid hormone excess and deficiency, including tachycardia, goiter, short stature, and attention deficit disorders. Diagnosis can be challenging due to the overlap with other thyroid disorders, making differential diagnosis essential for appropriate management.

Here we present a case of a 64-year-old man with a history of thyroidectomy for hyperthyroidism, who demonstrated persistent elevation of thyroid-stimulating hormone alongside high triiodothyronine and thyroxine levels despite ongoing levothyroxine therapy. The absence of pituitary abnormalities and the clinical profile led to the suspicion of resistance to thyroid hormone. This case highlights the importance of considering resistance to thyroid hormone in patients with atypical thyroid function tests and emphasizes the need for heightened awareness to ensure accurate diagnosis and effective treatment strategies.

Keywords: Resistance to thyroid hormone, Presentation, Diagnosis



INTRODUCTION

Resistance to thyroid hormone (RTH) is a rare genetic disorder characterized by reduced tissue responsiveness to thyroid hormone, primarily due to mutations in thyroid hormone receptor (THR) genes.[1] Affecting both genders equally, RTH has an estimated prevalence of 1 in 40,000 live births. Mutations in the THRB gene are the most common, leading to high serum free thyroxine (T4) and normal or mildly elevated thyroid-stimulating hormone (TSH) levels.[2] Clinical manifestations include sinus tachycardia, goiter, short stature, and attention deficit disorder. The diagnosis of RTH can be challenging due to its variable clinical presentation. However, clinicians should consider RTH when elevated serum free T4 levels are observed in conjunction with non-suppressed TSH levels. It is also essential to exclude other conditions that can present with similar laboratory findings, such as a TSH-secreting pituitary adenoma and familial dysalbuminemic hyperthyroxinemia. A definitive diagnosis can be made through genetic testing for mutations in the THR gene.

Management of RTH is tailored to the individual patient, focusing on alleviating symptoms caused by either thyroid hormone excess or deprivation. For instance, beta-blockers can be utilized to manage tachycardia. In cases of thyroid hormone deprivation, supra-physiological doses of levothyroxine may be administered, with close monitoring of growth and cognitive development. Regular monitoring and genetic counseling are recommended.[3] Here we present a case of RTH in an adult patient. The patient's data has been fully de-identified to protect his privacy and confidentiality.

CASE REPORT

A 64-year-old male who works as a business professional, claimed to be diagnosed with hypothyroidism after thyroidectomy in China and requested thyroxine treatment. His past medical history included hypertension, hyperlipidemia, and cerebral vascular disease. Amlodipine 5mg, Valsartan 160mg, and Bisoprolol 5mg daily for hypertension, Pravastatin 20mg daily for hyperlipidemia, and Clopidogrel 75mg daily for cerebral vascular disease, were prescribed for regular control. He had a surgical history of thyroidectomy for hyperthyroidism in 1990. The patient's family history was notable for thyroid disease; however, he reported that no specific treatment had been administered. He had a personal history of smoking one pack per day for 40 years, with no alcohol or betel nut use.

The patient reported that he did not follow thyroid function after thyroidectomy so that he did not take medication. However, elevated TSH levels were noted during annual health check-up in 2013, and persistently high TSH level was documented despite ongoing levothyroxine treatment (0.075mg daily) in China. Therefore, sella magnetic resonance imaging (MRI) was arranged in 2021, which revealed no pituitary tumor, so levothyroxine 0.075mg daily was continued. In July, 2023, he returned to Taiwan and came to our neurology outpatient department to request long-term medication. Levothyroxine 0.1mg daily was prescribed. Laboratory findings are presented in Table 1. TSH level was normal (3.45 ulU/ml, normal range: 0.53- 4.94 ulU/ml) but high triiodothyronine (T3) level (1.85 ng/ml, normal range: 0.64- 1.52 ng/ml) and T4 level (16.9 ug/dl, normal range: 4.9- 11.7 ug/dl) were found during follow-up. The dosage of levothyroxine was decreased to 0.05mg daily in the neurology outpatient department. However, high TSH (6.79 ulU/ml), T3 and T4 (1.94 ng/ml, 15.1 ug/dl, respectively) was noted again in January 2024, so he was subsequently transferred to our endocrine outpatient department for further management in April, 2024.

At the endocrine outpatient department, the patient claimed symptoms of occasional anxiety and palpitations, but denied symptoms such as fatigue, general weakness, decreased appetite, increased sensitivity to cold, dryness of skin, increased hair loss, hoarseness of voice, constipation, inexplicable weight gain, and edema. During the physical examination, the patient's measurements were as follows: height 173cm, weight 76kg, resulting in a body mass index of 25.3 kg/m2. Normal vital parameters (blood pressure 131/80 mmHg; pulse 78 bpm) were recorded. Neck examination showed a surgical scar at anterior midline and WHO grade 1 soft goiter without tenderness or redness. There was no periorbital puffiness, loss of the outer third of the eyebrows, or dry skin.

TSH, T3, and free T4 were rechecked by radioimmunoassay.(Table 2) The patient's TSH was 9.44 ulU/ml, T3 was 199.0 ng/dL (normal range: 72.0- 172.0 ng/dL)and free T4 was 1.15 ng/dL. Anti-thyroid peroxidase antibodies test showed negative result (<3.0 lU/mL). TSH receptor antibodies test showed positive result (22.1%, normal range: 0.0-15.0 %). Ultrasound imaging of the thyroid showed bilateral hypoechoic and heterogeneous patterns, compatible with residual tissues after thyroidectomy (Fig. 1). Levothyroxine was held for one month due to his symptoms of thyrotoxicosis. However, both TSH (11.37 ulU/ml) and T3 (1.94 ng/ml) remained elevated and free T4 (0.89 ng/dL)was within

normal range in May, 2024. We restarted levothyroxine 0.075mg daily and rechecked thyroid function one month later. TSH (6.48 ulU/ml) and T3 (1.87 ng/ml) was still high and free T4 (0.92 ng/dL) was within normal range. (Table 3) Pituitary function test was done and only mild decreased growth hormone, insulin-like growth factor 1 and testosterone was noted.

Therefore, the diagnosis was secondary hyperthyroidism, with the differential diagnosis including RTH and thyrotropin-secreting pituitary adenoma. RTH was highly suspected because no evidence of pituitary tumor was found on the sella MRI, though he did not do the genetic test. The treatment included adjustments of levothyroxine and ongoing follow-up at the endocrine outpatient department for monitoring thyroid and pituitary function.

This study was approved by Institution-al Ethics Review Board (permission number: 20250722R).

DISCUSSION

RTH is a rare genetic disorder characterized by reduced responsiveness of body tissues to thyroid hormone. The condition primarily arises from mutations in the thyroid hormone receptor (THR) genes, leading to varied clinical presentations.[1] RTH is a rare disorder with an estimated prevalence of 1 in 40,000 live births.[2] The condition affects both genders equally and can present at any age, though it is often diagnosed in childhood or adolescence during evaluations for growth or developmental delays.[4]

The primary cause of RTH is mutations in the THRB gene, and mutations in the THR alpha (THRA) gene have also been identified. Generally, a single copy of the mutated gene is sufficient to cause disease, and RTHβ is inherited in an autosomal dominant fashion. This suggests that the pathogenesis of the disease is driven by dominant-negative inhibition of wild-type THRB.[1] Patients with mutations in THRB, typically characterized by high serum free iodothyronine levels (principally free T4) and TSH concentration is either within the normal range or mildly elevated. Individuals with RTHβ maintain a nearly euthyroid state compensated by the high thyroid hormone level in concert with the tissue expression level of the mutant receptor.[5] Thus, features of thyroid hormone excess and deficiency may coexist, producing sinus tachycardia in the heart and goiter by TSH stimulation, while the pituitary expresses mainly THRB including the mutant form. Short stature, attention deficit disorder may also occur.[2]

Patients with mutations in THRA gene leading to RTHα have been reported.[3] The patients with RTHα may present with delayed growth, tooth eruption, severe constipation, decreased muscle tone, and impaired motor skills. These patients typically exhibit minimal effects on the hypothalamic-pituitary-thyroid axis, with TSH levels within the normal range, slightly lower free T4 levels, and slightly higher total T3 levels.[6]

Differential diagnosis is essential to distinguish RTH from other conditions with similar biochemical profiles, such as thyrotropin-secreting pituitary adenomas and familial dysalbuminemic hyperthyroxinemia.[7] A family history of thyroid disorders and the presence of similar symptoms in relatives may support the diagnosis. The use of a diagnostic algorithm involving thyroid function tests and genetic analysis is recommended to confirm RTH and exclude other conditions.

No specific therapy currently exists to fully correct RTH. Mutation-specific ligands, such as thyroid hormone analogues, have shown potential in vitro but remain untested in vivo.[2] Management is tailored to alleviate symptoms caused by either thyroid hormone excess or deprivation. For tachycardia, we could utilize beta-blockade. For thyroid hormone deprivation, we could administer supra-physiologic doses of levothyroxine and monitor growth and cognitive development closely. Higher levothyroxine doses may be necessary when congenital hypothyroidism and/or ectopic thyroid tissue coexist.[8]

Regular follow-up is crucial for patients with RTH. Monitoring should include thyroid function tests to adjust medication dosages and ensure biochemical control, as well as periodic clinical evaluations of growth, development, and cognitive function, particularly in pediatric patients. Given the hereditary nature of the disorder, genetic counseling for family members may be beneficial.[2]

This case highlights the clinical importance of understanding RTH. The thyroid function tests in patients with RTH can be misinterpreted as primary hyperthyroidism or hypothyroidism, potentially leading to inappropriate treatments. Consequently, patients with RTH may undergo unnecessary procedures such as radioactive iodine ablation or thyroid surgery.[3]

Recently, selective thyromimetics that target the THRB nuclear receptor, such as Resmetirom, have shown promise in improving metabolic dysfunction-associated steatotic liver disease in a large phase III trial.[9] This development suggests that future research into agents that directly target the thyroid hormone receptor is warranted to determine if they could fully

correct the underlying defects in RTH.

This case report has several inherent limitations. The primary limitation is the lack of generalizability. As a report of a single patient, these findings are not necessarily representative of other individuals with RTH. Secondly, endocrine dynamic tests, such as a TRH stimulation test or a T3 suppression test, were not performed because the necessary agents were unavailable at our institution. Therefore, a thyrotropin-secreting pituitary adenoma could not be definitively excluded. Finally, while the clinical presentation is highly suggestive of RTH, a genetic test, which was not performed, would be essential for a definitive diagnosis.

CONCLUSIONS

RTH is a rare genetic disorder primarily caused by mutations in the thyroid hormone receptor genes, particularly the THRB gene. This disorder presents with a unique clinical profile that includes both thyroid hormone deficiency and excess, requiring careful differential diagnosis to distinguish it from other thyroid-related conditions.

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TABLES

Table 1. Summary of thyroid function tests and levothyroxine dosage

Date	Levothyroxine Dosage (mg/day)	TSH (μIU/mL)[1]	T3 (ng/mL)[2]	T4 (μg/dL)[3]
November 2023	0.10	3.45	1.85	16.9
January 2024	0.05	6.79	1.94	15.1

[1] Normal range: 0.53–4.94 μIU/mL

[2] Normal range: 0.64–1.52 ng/mL

[3] Normal range: 4.9–11.7 μg/dL

Table 2. Laboratory results from radioimmunoassay

Date	TSH (μIU/mL)[1]	T3 (ng/dL)[2]	Free T4 (ng/dL)[3]	Anti-TPO Antibodies (IU/mL)[4]	TSH Receptor Antibodies (%)[5]
April 2024	9.44	199.0	1.15	<3.0 (Negative)	22.1

[1] Normal range: 0.53–4.94 μIU/mL

[2] Normal range: 72.0–172.0 ng/dL

[3] Normal range: 0.8–1.8 ng/dL

[4] Normal range: <3.0 IU/mL

[5] Normal range: 0.0–15.0 %

Table 3. Follow-up thyroid function tests and levothyroxine adjustments

Date	Levothyroxine Dosage (mg/day)	TSH (μIU/mL)[1]	T3 (ng/mL)[2]	Free T4 (ng/dL)[3]
May 2024	0.00	11.37	1.94	0.89
June 2024	0.075	6.48	1.87	0.92

[1] Normal range: 0.53–4.94 μIU/mL

[2] Normal range: 0.64–1.52 ng/mL

[3] Normal range: 0.8–1.8 ng/dL

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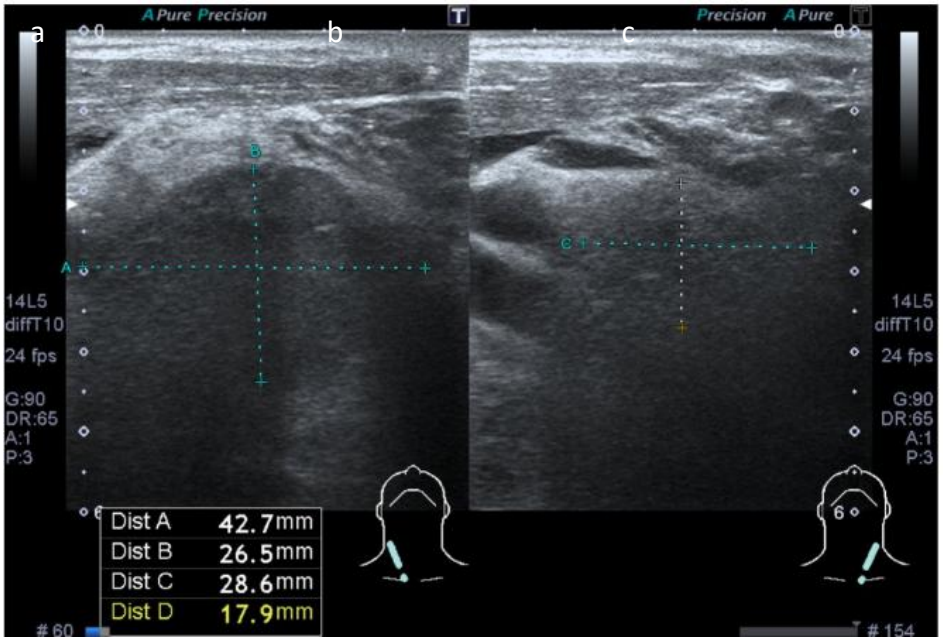
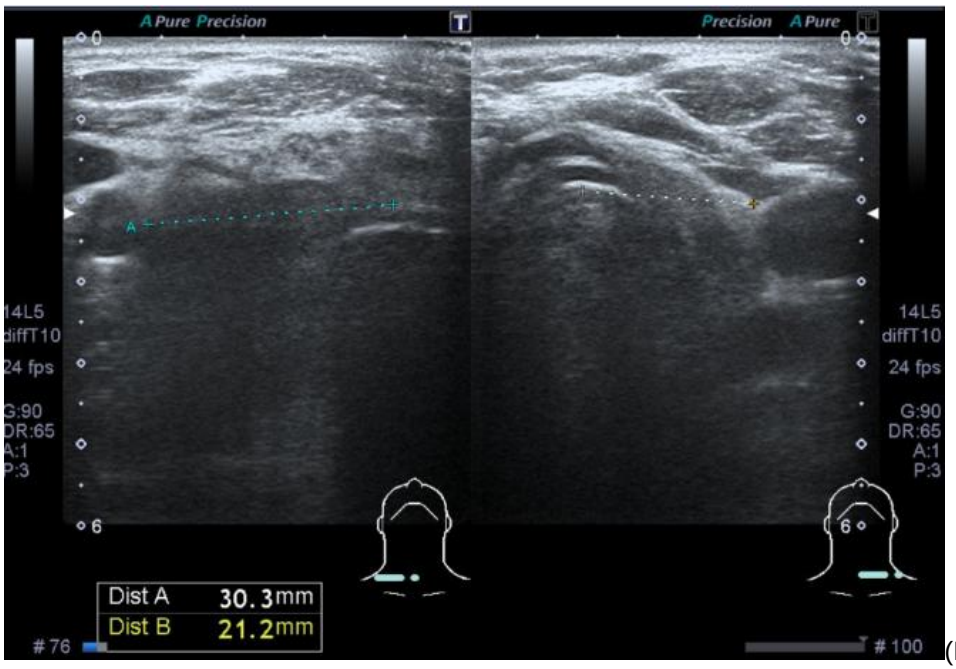


(A)



(B)

Figure 1. Ultrasound of the thyroid in April 2024. The bilateral lobes of the thyroid appeared hypoechoic and heterogeneous, findings compatible with residual tissue after thyroidectomy. (A) Longitudinal view. (B) Transverse view.

Resistance to thyroid hormone: A case report and the literatures review

甲狀腺激素抗性症：一病例報告與文獻回顧

劉定昕[1]　陳佩綺[1,*]

中文摘要

甲狀腺激素抗性症（Resistance to thyroid hormone, RTH）是一種罕見的遺傳性疾病，主要由於甲狀腺素受體基因突變，導致組織對甲狀腺素反應降低。此疾病特徵為血清中游離三碘甲狀腺素（free T3）及甲狀腺素（free T4）濃度升高，但甲狀腺刺激素（TSH）濃度正常或輕度升高。臨床上，患者可能同時表現出甲狀腺素過多與不足的症狀，例如心跳過快、甲狀腺腫大、身材矮小與注意力不足等。由於本病與其他甲狀腺疾病在臨床表現與實驗室數值上有所重疊，診斷上具有挑戰性，因此進行鑑別診斷對於後續治療至關重要。

本報告描述一名 64 歲男性，因過去甲狀腺機能亢進接受甲狀腺切除手術，術後持續接受左旋甲狀腺素（levothyroxine）治療，但血中 TSH 濃度持續偏高，且 free T3 與 free T4 亦異常升高。影像學並未發現腦下垂體異常，且整體臨床表現高度懷疑甲狀腺激素抗性症。本病例提醒臨床醫師，對於出現非典型甲狀腺功能異常的患者，應納入甲狀腺激素抗性症的考量，以提高診斷準確性並制定適當的治療策略。

關鍵字：甲狀腺激素抗性症、臨床表現、診斷

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