Artikel Penelitian

EXPLORING THE ROLE OF APOLIPOPROTEIN A AS A PREDICTIVE BIOMARKER FOR FECAL INCONTINENCE SEVERITY IN THE ELDERLY: A FOCUS ON LIPID-IMMUNE INTERACTIONS

Bryan Anna Wijaya, Peter Ian Limas*, Yohanes Firmansyah, Triyana Sari, Alexander Halim Santoso

Faculty of Medicine, University of Tarumanagara

Letjen S. Parman St No.1, RT.6/RW.16, Tomang, Grogol petamburan, West Jakarta City, Jakarta

*Email: peterl@fk.untar.ac.id

Abstract

Fecal incontinence (FI) is a common problem among the elderly, affecting their quality of life. Identifying reliable biomarkers like Apolipoprotein A (Apo-A) could improve management strategies, as its anti-inflammatory properties may help predict the severity of FI. This study aims to assess Apo-A as a lipid biomarker for predicting the severity of fecal incontinence, using the Fecal Incontinence Severity Index (FISI) for measurement. This cross-sectional study involved 93 elderly participants at Bina Bhakti Nursing Home, who exhibited varying FI levels. The severity was evaluated using the FISI, while serum lipid profiles were analyzed to measure Apo-A levels. We assessed Apo-A's predictive ability for FI severity through the area under the curve (AUC) from the receiver operating characteristic (ROC) curve. The state variable was set at 0 on the FISI scale, indicating the absence of FI. The AUC for Apo-A was found to be 0.631, with a p-value of 0.031, indicating that higher Apo-A levels are significantly linked to the absence of fecal incontinence. Apo-A is a promising biomarker for predicting FI severity, although its predictive capacity is limited. Future studies should investigate combining Apo-A with other inflammatory markers to enhance prediction accuracy.

Keywords: *Apolipoprotein A, elderly, fecal incontinence*

INTRODUCTION

Fecal incontinence (FI) refers to the involuntary loss of control over bowel movements, significantly affecting an individual's quality of life. It is estimated to affect 7-15% of the general population. (Dexter *et al*., 2024) A comprehensive review and meta-analysis of 80 studies, encompassing data from 548,316 individuals, revealed that FI is more common among older adults aged 60 and above, with a global prevalence of 9.3% (95% CI, 6.6%–12.0%). This rate is nearly double that observed in younger individuals, with a prevalence of 4.9% (95% CI, 2.9%–6.9%). Older adults are 1.75 times more likely to experience FI than their younger counterparts (OR, 1.75; 95% CI, 1.39–2.20). (Mack *et al*., 2024)

Fecal incontinence can have a profound impact on individuals, leading to both physical and emotional challenges. Physically, it can cause recurring infections, skin ulcers, and scarring, while emotionally, it often results in social anxiety, behavioral difficulties, isolation, and a loss of self-esteem. These challenges can create guilt and shame that further diminish the quality of life. Among older adults, the high prevalence of FI significantly affects their overall well-being, contributing to increased rates of illness and even mortality. (Bharucha *et al*., 2017; Jamieson *et al*., 2017; Loganathan *et al*., 2021; Rajindrajith *et al*., 2021) Among its leading causes are surgical procedures, such as internal sphincterotomy and fistulotomy, which are responsible for 35–45% of cases. However, FI often arises from other factors, including severe constipation leading to fecal impaction, overuse of laxatives, diarrhea, cognitive decline, aging-related changes, and

neuromuscular conditions like autonomic neuropathy in older adults. (Akhtar & Padda, 2005; Lumban Gaol *et al*., 2024)

Chronic inflammation can also significantly contribute to the development of fecal incontinence in older adults, primarily by weakening the anal sphincter muscles and surrounding tissues. Persistent inflammation in the anorectal area can gradually damage these structures, worsening the condition. Apolipoprotein A (Apo-A), known for its anti-inflammatory and antioxidant properties, plays a key role in regulating inflammation. When Apo-A levels are particularly low, it is often linked to systemic inflammation and metabolic issues, which can intensify localized inflammation in the anorectal region. This increased inflammation hampers tissue healing and further compromises the sphincter, raising the risk of fecal incontinence in elderly individuals. (Barter *et al*., 2004; Daniil *et al*., 2011; Georgila *et al*., 2019; Sirniö *et al*., 2017; Vuilleumier *et al*., 2013)

High levels of Apo-A play a vital role in protecting against fecal incontinence by supporting several key processes. Apo-A helps control chronic inflammation, reduces oxidative stress, and promotes the health of blood vessels, nerves, and tissues, all of which are essential for maintaining the strength and function of the anorectal region. It works by preventing the activation of macrophages and lowering the production of proinflammatory cytokines like TNF-α, IL-6, and IL-1β, factors that can weaken the anal sphincter and surrounding tissues. Apolipoprotein A also blocks the NF-κB signaling pathway, a major driver of inflammation, which helps reduce immune cell activity and further tissue damage. These protective effects are particularly critical for older adults, who are more vulnerable to fecal incontinence. (Patel *et al*., 2010; Tao *et al*., 2024; Vuilleumier *et al*., 2013)

There hasn't been much research discussing Apo-A levels in the blood as a biomarker predictor of fecal incontinence in the geriatric population in Indonesia. Our study aims to explore the potential of Apo-A as a predictive biomarker for this condition. By identifying its role, we hope to contribute to strategies that prevent or minimize the risk of fecal incontinence in older individuals, ultimately improving their quality of life and well-being.

METHODS

Research Design and Sampling

This research applied a cross-sectional design as an analytical observational study conducted in May 2024. A total of 93 elderly residents at Bina Bhakti Nursing Home were examined using total sampling. These participants exhibited varying levels of fecal incontinence severity and met the established inclusion and exclusion criteria. Eligibility for inclusion required participants to be at least 60 years of age and to consent to interviews. Exclusions applied to individuals who lacked cooperation or who could not understand the Indonesian language.

Research Variables and Instruments

The research variables comprise two components: apo-A and fecal incontinence. Apolipoprotein A levels from venous blood were analyzed using an immunoturbidimetric method for measuring Apo-A in serum works by detecting changes in turbidity when Apo-A interacts with specific antibodies. Blood is collected after an overnight fast and the serum is separated through centrifugation. The serum is then mixed with a reagent containing antibodies that bind to Apo-A, forming complexes that make the solution cloudy. This turbidity is measured using a specialized analyzer and the Apo-A levels are determined by comparing the results to a standard calibration curve. (Riepponen *et al*., 1987)

Fecal incontinence was determined with the Fecal Incontinence Severity Index (FISI) questionnaire, a widely used assessment tool to identify symptoms of fecal incontinence in older adults. This questionnaire assesses the severity of fecal incontinence by examining four common types of leakage experienced in affected populations: gas, mucus, liquid stool, and solid stool. The frequency of these leakage events is categorized into five levels ranging from one to three times

per month to once or twice per week or day, providing a comprehensive view of the incontinence patterns. This scoring system ranges from 0 to 61, with higher scores reflecting greater severity of fecal incontinence. A minimum score of 0 indicates no fecal incontinence, while a maximum score of 61 denotes severe fecal incontinence. (Rockwood *et al*., 1999) (Table 1)

Table 1. Fecal Incontinence Severity Index

Incontinent to Gas	Incontinent for Liquid Stool
Never (0 points)	Never (0 points)
1 to 3 times per month (4 points)	1 to 3 times per month (8 points)
1 time per week (6 points)	1 time per week (10 points)
2 or more times per week (8 points)	2 or more times per week (13 points)
1 time per day (11 points)	1 time per day (17 points)
2 or more times per day (12 points)	2 or more times per day (19 points)
Incontinent for Mucus	**Incontinent for Solid Stool**
Never (0 points)	Never (0 points)
1 to 3 times per month (3 points)	1 to 3 times per month (8 points)
1 time per week (5 points)	1 time per week (10 points)
2 or more times per week (7 points)	2 or more times per week (13 points)
1 time per day (10 points)	1 time per day (16 points)
2 or more times per day (12 points)	2 or more times per day (18 points)

Statistical Analysis

Receiver Operating Characteristic (ROC) analysis was conducted in this study to assess the effectiveness of Apo-A levels in predicting fecal incontinence severity. The ROC curve provided a visual representation of sensitivity and specificity at various Apo-A thresholds, allowing for the identification of an optimal cutoff level that could potentially predict or reduce the risk of fecal incontinence. The area under the curve (AUC) was calculated to measure the diagnostic accuracy of Apo-A, indicating its capability to distinguish between individuals with and without fecal incontinence. A Fecal Incontinence Severity Index (FISI) score of 0 was applied as the standard to signify the absence of fecal incontinence.

RESULTS AND DISCUSSION

This study included 93 elderly participants with an average age of 74.19 years. Most participants were female, making up 82.8% of the group. The average Apolipoprotein-A (Apo-A) level among the elderly was 155.59 mg/dL and additionally, the Fecal Incontinence Severity Index (FISI) scores showed an average of 14.35 across participants. (Table 2)

Table 2. Characteristics of Research Results

Parameter	N (%)	Mean (SD)	Med (Min-Max)
Age	93 (100%)	74.19 (7.95)	75 (61 – 97)
Gender			
Male	16 (17.2%)		
Female	77 (82.8%)		
Apolipoprotein-A		155.59 (15.66)	154 (115 – 199)
Fecal Incontinence			
Yes	40 (43%)		
No	53 (57%)		
Fecal Incontinence Severity Index (FISI)		14.35 (19.97)	0 (0 – 61)

The ROC analysis reveals that Apolipoprotein-A is a notable predictor of fecal incontinence severity, demonstrated by an AUC of 0.631. This AUC indicates that Apo-A has a moderate predictive ability in distinguishing between the elderly with and without fecal incontinence. The 95% confidence interval (CI) for the AUC ranging from 0.516 to 0.746, suggests that Apo-A's predictive capacity ranges from moderate to potentially high within the elderly population. Additionally, the p-value of 0.031 reinforces the statistical significance of the association between elevated Apo-A levels and reduced severity of fecal incontinence. Together, these findings underscore the potential clinical value of Apo-A as a meaningful biomarker for managing fecal incontinence among older adults. (Table 3 and Figure 1)

Table 3. Area Under Curve (AUC) of Apo-A as a Predictor of Fecal Incontinence

Area	Std. Error	*p-value*	95% Confidence Interval	
			Lower	Upper
0.631	0.059	0.031	0.516	0.746

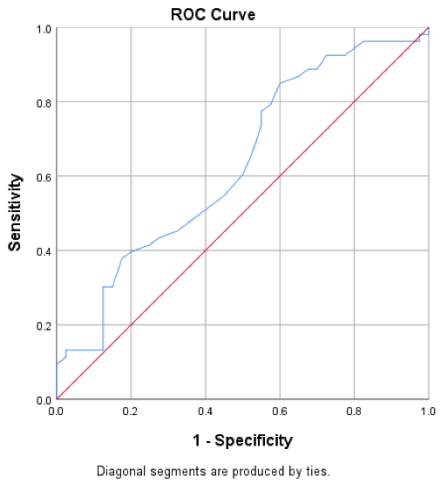

Figure 1. Receiver Operating Characteristic (ROC) Curve of Apo-A as a Predictor of Fecal Incontinence

These findings reveal a correlation between Apo-A levels and fecal incontinence severity, highlighting the importance of anti-inflammatory response regulation in managing anorectal health among older adults. This relationship illustrates the complex interplay between inflammation and anorectal function, emphasizing the necessity for further investigation into the mechanisms that connect Apo-A levels with the severity of fecal incontinence.

Rectal inflammation can significantly increase fecal incontinence risk by disrupting the rectum's normal sensory and motor functions. Inflammatory processes heighten the sensitivity of rectal afferent pathways, leading to an exaggerated perception of urgency even with minimal stool presence. Concurrently, inflammation induces hypercontractility of rectal muscles, exacerbating urgency and increasing the frequency of bowel movements. This dual disruption results in impaired bowel regulation and a heightened risk of involuntary stool leakage. (Hayden & Weiss, 2011; Kamal *et al*., 2021; Knowles *et al*., 2022; Lunniss *et al*., 2004)

This dysfunction is frequently observed in conditions such as inflammatory bowel disease (IBD) and other chronic gastrointestinal disorders, where ongoing inflammation is closely linked to the onset of fecal incontinence. Persistent inflammation in these conditions has been associated with a variety of anorectal impairments, including reduced rectal sensation, compromised rectal distensibility, diminished anal resting pressure, and the loss of the anorectal inhibitory reflex. These factors collectively disrupt normal bowel control, making it more difficult for individuals to manage bowel movements effectively. As inflammation damages the tissues and nerves involved in bowel regulation, it contributes significantly to the progression and severity of fecal incontinence. In these cases, the impact of inflammation extends beyond localized tissue damage, affecting the rectum

and anorectal coordination and overall bowel function. The ongoing inflammatory process can disrupt normal sensory and motor responses, impairing the regulation of bowel movements. (Hayden & Weiss, 2011; Kamal *et al*., 2021; Knowles *et al*., 2022)

Furthermore, the inflammatory cascade involves key cytokines such as TNF-α, IL-6, and IL-1β, which significantly promote tissue damage and hinder the healing process. Aging exacerbates this by promoting a more pro-inflammatory state, which disrupts the peripheral immune system and triggers excessive innate immune activity. This results in the release of more pro-inflammatory cytokines and a reduction in anti-inflammatory cytokines, further intensifying inflammation. (Tylutka *et al*., 2024) Additionally, NF-κB, a protein complex that regulates genes, plays a crucial role in the development and progression of inflammation by controlling the expression of these cytokines. Together, these factors contribute to prolonged inflammation, making it more difficult to repair tissue and increasing the risk of chronic inflammation, particularly in older adults. (Liu *et al*., 2017)

As an anti-inflammatory, Apolipoprotein A reduces inflammation by reducing the production of pro-inflammatory cytokines. This anti-inflammatory action is primarily achieved through its ability to regulate immune cell activity and modulate key inflammatory pathways. By interacting with macrophages and other immune cells, Apo-A inhibits the release of cytokines such as TNF-α, IL-6, and IL-1β, which are central to driving chronic inflammation. This mechanism helps to suppress excessive immune responses, reduce tissue damage, and create a more favorable environment for tissue repair. In the context of rectal inflammation, Apo-A's regulatory effects are particularly significant. By mitigating inflammation and preventing its chronic progression, Apo-A contributes to preserving tissue integrity and neuromuscular coordination. (Georgila *et al*., 2019; Kamal *et al*., 2021; Knowles *et al*., 2022; Tao *et al*., 2024; Vuilleumier *et al*., 2013)

This highlights the potential of Apo-A as a valuable biomarker for predicting fecal incontinence, particularly in inflammatory conditions. Elevated levels of Apo-A appear to offer protective effects against fecal incontinence, emphasizing its importance in maintaining anorectal health. Regular screening to monitor Apo-A levels could facilitate early detection and timely intervention, enabling more effective management of fecal incontinence. (Georgila *et al*., 2019; Knowles *et al*., 2022; Ruslim *et al*., 2024)

This study has several limitations that should be acknowledged. First, its cross-sectional design limits the ability to establish causal relationships between Apo-A levels and the severity of fecal incontinence, as the findings represent associations rather than definitive cause-and-effect connections. Second, the research was conducted exclusively on elderly residents of a single nursing home, which restricts the generalizability of the results to broader and more diverse populations. Lastly, the study focused solely on Apo-A as a biomarker without examining its interactions with other inflammatory markers or pathways. Future research for exploring these interactions could provide a more comprehensive understanding of the role of Apo-A in the pathophysiology of fecal incontinence and enhance the predictive value of the findings. Future studies should aim to address these limitations to improve the clinical applicability of Apo-A as a predictive biomarker.

CONCLUSION

Apo-A levels may serve as a potential biomarker for the risk of fecal incontinence in the elderly. By regularly monitoring Apo-A, healthcare providers could better identify individuals at risk, enabling earlier interventions to improve fecal incontinence and overall health outcomes. This proactive approach may help reduce the severity of fecal incontinence and prevent related complications.

REFERENCES

Akhtar, A. J., & Padda, M. (2005). Fecal incontinence in older patients. *Journal of the American Medical Directors Association*, *6*(1), 54–60. https://doi.org/10.1016/j.jamda.2004.12.012

Barter, P. J., Nicholls, S., Rye, K.-A., Anantharamaiah, G. M., Navab, M., & Fogelman, A. M. (2004). Antiinflammatory Properties of HDL. *Circulation Research*, *95*(8), 764–772. https://doi.org/10.1161/01.RES.0000146094.59640.13

Bharucha, A. E., Rao, S. S. C., & Shin, A. S. (2017). Surgical Interventions and the Use of Device-Aided Therapy for the Treatment of Fecal Incontinence and Defecatory Disorders. *Clinical Gastroenterology and Hepatology*, *15*(12), 1844–1854. https://doi.org/10.1016/j.cgh.2017.08.023

Daniil, G., Phedonos, A. A. P., Holleboom, A. G., Motazacker, M. M., Argyri, L., Kuivenhoven, J. A., & Chroni, A. (2011). Characterization of antioxidant/anti-inflammatory properties and apoA-I-containing subpopulations of HDL from family subjects with monogenic low HDL disorders. *Clinica Chimica Acta*, *412*(13–14), 1213–1220. https://doi.org/10.1016/j.cca.2011.03.011

Dexter, E., Walshaw, J., Wynn, H., Dimashki, S., Leo, A., Lindsey, I., & Yiasemidou, M. (2024). Faecal incontinence—a comprehensive review. *Frontiers in Surgery*, *11*. https://doi.org/10.3389/fsurg.2024.1340720

Georgila, K., Vyrla, D., & Drakos, E. (2019). Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and Cancer. *Cancers*, *11*(8), 1097. https://doi.org/10.3390/cancers11081097

Hayden, D., & Weiss, E. (2011). Fecal Incontinence: Etiology, Evaluation, and Treatment. *Clinics in Colon and Rectal Surgery*, *24*(01), 064–070. https://doi.org/10.1055/s-0031-1272825

Jamieson, H. A., Schluter, P. J., Pyun, J., Arnold, T., Scrase, R., Nisbet-Abey, R., Mor, V., Deely, J. M., & Gray, L. (2017). Fecal Incontinence Is Associated With Mortality Among Older Adults With Complex Needs: An Observational Cohort Study. *American Journal of Gastroenterology*, *112*(9), 1431–1437. https://doi.org/10.1038/ajg.2017.200

Kamal, N., Motwani, K., Wellington, J., Wong, U., & Cross, R. K. (2021). Fecal Incontinence in Inflammatory Bowel Disease. *Crohn's & Colitis 360*, *3*(2). https://doi.org/10.1093/crocol/otab013

Knowles, C. H., Dinning, P., Scott, S. M., Swash, M., & de Wachter, S. (2022). New concepts in the pathophysiology of fecal incontinence. *Annals of Laparoscopic and Endoscopic Surgery*, *7*, 15–15. https://doi.org/10.21037/ales-2022-02

Liu, T., Zhang, L., Joo, D., & Sun, S.-C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy*, *2*(1), 17023. https://doi.org/10.1038/sigtrans.2017.23

Loganathan, A. K., Mathew, A. S., & Kurian, J. J. (2021). Assessment of Quality of Life and Functional Outcomes of Operated Cases of Hirschsprung Disease in a Developing Country. *Pediatric Gastroenterology, Hepatology & Nutrition*, *24*(2), 145. https://doi.org/10.5223/pghn.2021.24.2.145

Lumban Gaol, L., Purba, A., Diposarosa, R., & Pratiwi, Y. (2024). Role of Hypoxic Secretome from Mesenchymal Stem Cells in Enhancing Tissue Repair: Regulatory Effects on HIF-1α, VEGF, and Fibroblast in a Sphincterotomy Rat Model. *Journal of Inflammation Research*, *Volume 17*, 7463–7484. https://doi.org/10.2147/JIR.S480061

Lunniss, P. J., Gladman, M. A., Hetzer, F. H., Williams, N. S., & Scott, S. M. (2004). Risk Factors in Acquired Faecal Incontinence. *Journal of the Royal Society of Medicine*, *97*(3), 111–116. https://doi.org/10.1177/014107680409700303

Mack, I., Hahn, H., Gödel, C., Enck, P., & Bharucha, A. E. (2024). Global Prevalence of Fecal Incontinence in Community-Dwelling Adults: A Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology*, *22*(4), 712-731.e8. https://doi.org/10.1016/j.cgh.2023.09.004

Patel, S., Di Bartolo, B. A., Nakhla, S., Heather, A. K., Mitchell, T. W., Jessup, W., Celermajer, D. S., Barter, P. J., & Rye, K.-A. (2010). Anti-inflammatory effects of apolipoprotein A-I in the rabbit. *Atherosclerosis*, *212*(2), 392–397. https://doi.org/10.1016/j.atherosclerosis.2010.05.035

Rajindrajith, S., Devanarayana, N. M., Thapar, N., & Benninga, M. A. (2021). Functional Fecal Incontinence in Children. *Journal of Pediatric Gastroenterology and Nutrition*, *72*(6), 794–801. https://doi.org/10.1097/MPG.0000000000003056

Riepponen, P., Marniemi, J., & Rautaoja, T. (1987). Immunoturbidimetric determination of apolipoproteins A-1 and B in serum. *Scandinavian Journal of Clinical and Laboratory Investigation*, *47*(7), 739–744. http://www.ncbi.nlm.nih.gov/pubmed/3685874

Rockwood, T. H., Church, J. M., Fleshman, J. W., Kane, R. L., Mavrantonis, C., Thorson, A. G., Wexner, S. D., Bliss, D., & Lowry, A. C. (1999). Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence. *Diseases of the Colon & Rectum*, *42*(12), 1525–1531. https://doi.org/10.1007/BF02236199

Ruslim, W. H., Santoso, A. H., Kurniawan, J., Destra, E., Setiawan, F. V., & Wijaya, B. A. (2024). Peningkatan Kewaspadaan terhadap Hiperlipidemia Melalui Pemeriksaan Kadar Kolesterol pada Kelompok Lanjut Usia di Panti Werda Hana. *Jurnal Pelayanan Dan Pengabdian Masyarakat Indonesia*, *3*(2), 01–06. https://doi.org/10.55606/jppmi.v3i2.1227

Sirniö, P., Väyrynen, J. P., Klintrup, K., Mäkelä, J., Mäkinen, M. J., Karttunen, T. J., & Tuomisto, A. (2017). Decreased serum apolipoprotein A1 levels are associated with poor survival and systemic inflammatory response in colorectal cancer. *Scientific Reports*, *7*(1), 5374. https://doi.org/10.1038/s41598-017-05415-9

Tao, X., Tao, R., Wang, K., & Wu, L. (2024). Anti-inflammatory mechanism of Apolipoprotein A-I. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1417270

Tylutka, A., Walas, Ł., & Zembron-Lacny, A. (2024). Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1330386

Vuilleumier, N., Dayer, J., Von, E., & Roux-Lombard, P. (2013). Pro- or anti-inflammatory role of apolipoprotein A-1 in high-density lipoproteins? *Swiss Medical Weekly*. https://doi.org/10.4414/smw.2013.13781