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Oxidative Stress and Renal Dysfunction in Lincomycin-Induced Nephrotoxicity: Evaluating the Therapeutic Potential of Activated Charcoal

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Abstract

Background: The kidneys play a vital role in homeostasis and metabolic waste elimination, but they are highly susceptible to toxic insults due to their role in drug metabolism. Lincomycin, a lincosamide antibiotic, has been implicated in nephrotoxicity through oxidative stress-mediated mechanisms, leading to renal dysfunction. Activated charcoal, a widely used adsorbent, has shown potential in mitigating renal damage by adsorbing toxins and modulating oxidative stress. However, its efficacy in lincomycin-induced nephrotoxicity remains poorly understood. ***Aim:*** This study investigates the protective potential of activated charcoal against lincomycin-induced nephrotoxicity by assessing oxidative stress markers, renal function indices, and histopathological changes. ***Methodology:*** Twenty-five (25) Wistar rats were divided into five groups (n=5). Group I (Control) received normal saline, while Group II received lincomycin (200 mg/kg). Groups III, IV, and V were co-administered lincomycin with varying percentages of activated charcoal (25%, 50%, and 75%). Kidney function markers (creatinine, urea), oxidative stress indices (Superoxide Dismutase [SOD], Malondialdehyde [MDA]), and histopathological changes were evaluated. ***Results:*** Lincomycin administration significantly reduced creatinine (0.59±0.07 mg/dl) and urea (19.85±2.11 mg/dl) compared to controls (0.85±0.04 mg/dl, 25.78±1.19 mg/dl; $P<0.05$). Oxidative stress was evident in the lincomycin group, with a decrease in SOD (14.25±1.81 U/mg protein) and an increase in MDA. Activated charcoal co-administration mitigated these effects, improving kidney function and oxidative stress parameters. ***Conclusion:*** Activated charcoal offers protective effects against lincomycin-induced nephrotoxicity by reducing oxidative stress and preserving renal function. Its potential as an adjunct therapy in mitigating antibiotic-induced kidney damage warrants further investigation.

Keywords: nephrotoxicity, lincomycin, activated charcoal, oxidative stress, renal dysfunction, antioxidant therapy

1. Introduction

The kidneys are vital organs that play a critical role in human physiology by maintaining fluid and electrolyte homeostasis, regulating blood pressure, supporting erythropoiesis, and ensuring efficient waste elimination. They are structurally adapted for filtration and selective reabsorption, which are crucial processes in metabolic waste removal and acid-base balance (Lote, 2012). Despite their anatomical and physiological significance, the kidneys are highly susceptible to toxic insults due to their role in drug metabolism and excretion. Nephrotoxicity, a condition characterized by kidney dysfunction caused by exposure to harmful substances, has emerged as a major concern in pharmacotherapy, particularly in the context of antibiotics and other nephrotoxic agents (Wang

et al., 2021).

Among nephrotoxic antibiotics, lincomycin, a lincosamide antibiotic primarily used for treating serious bacterial infections, has been associated with adverse renal effects (Liu *et al*., 2011). While lincomycin is often reserved for cases where penicillin is contraindicated, its potential to induce nephrotoxicity through oxidative stress and inflammatory pathways is an area of growing concern (Zhang *et al*., 2022). Lincomycin-induced nephrotoxicity is thought to result from mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and subsequent oxidative damage to renal cells. Long-term exposure to lincomycin may exacerbate kidney injury by impairing antioxidant defense mechanisms, leading to structural and functional deterioration of the renal parenchyma (Chen *et al*., 2023).

Oxidative stress is a well-recognized pathological mechanism underlying kidney injury, contributing to renal inflammation, apoptosis, and fibrosis. Excessive Reactive Oxygen Species (ROS) production can overwhelm the antioxidant capacity of renal cells, resulting in lipid peroxidation, protein oxidation, and DNA damage (Gong *et al*., 2021). The role of oxidative stress in nephrotoxicity has been widely studied, with recent evidence highlighting the importance of therapeutic strategies that target ROS neutralization to mitigate renal damage (Huang *et al*., 2022). This has led to increased interest in natural and synthetic antioxidants as potential nephroprotective agents.

Activated charcoal, a well-known adsorbent with a high surface area and strong binding capacity, has been explored for its detoxification properties in various clinical settings (Zhao *et al*., 2023). Traditionally used for treating poisonings and overdoses, activated charcoal functions by binding to toxins in the gastrointestinal tract, preventing their systemic absorption and facilitating their excretion (WHO, 2009). Recent studies suggest that activated charcoal may also have renoprotective effects by adsorbing uremic toxins and reducing oxidative stress markers in renal dysfunction (Sharma *et al*., 2020). Its ability to modulate the gut-kidney axis and reduce systemic inflammation further underscores its potential as an adjunct therapy in kidney-related disorders (Kim *et al*., 2021).

Despite the known nephrotoxic effects of lincomycin and the emerging interest in activated charcoal as a potential nephroprotective agent, there is limited research evaluating its efficacy in mitigating lincomycin-induced renal injury. Current studies have primarily focused on the role of antioxidants and adsorbents in general nephrotoxicity models, leaving a gap in understanding their specific impact on lincomycin-induced oxidative stress and renal dysfunction. Additionally, while oxidative stress has been implicated in various nephropathies, its precise contribution to lincomycin-induced nephrotoxicity and the extent to which activated charcoal can counteract these effects remain unclear (Zhao *et al*., 2023).

This study aims to bridge this gap by evaluating the therapeutic potential of activated charcoal in lincomycin-induced nephrotoxicity. By investigating key oxidative stress markers, renal function indices, and histopathological changes, this research seeks to provide insights into the protective mechanisms of activated charcoal against antibiotic-induced renal damage. The findings from this study will not only contribute to the existing body of knowledge on nephrotoxicity mitigation but also offer a potential therapeutic strategy for preserving kidney function in patients undergoing lincomycin therapy. Given the increasing prevalence of antibiotic-associated kidney injury, identifying effective interventions to prevent or reverse renal dysfunction is of paramount clinical significance.

2. Materials & Methodology

2.1 Experimental Animals

Twenty-five (25) healthy adult male Wistar rats, weighing between 135.4 and 159.9 g, were procured for the study. The animals were housed in the Animal House of the College of Health Sciences, Benue State University, Makurdi. They were acclimatized for fourteen (14) days before the commencement of the experiment. The rats were randomly assigned into five (5) groups, with five (5) rats per group, and housed in plastic cages under standard laboratory conditions at a temperature of 28-31°C. They were provided with standard vital rat feed and water *ad libitum* throughout the experimental period.

2.2 Experimental Drug

Lincomycin capsules were obtained from Mernax Pharmacy, opposite the College of Health Sciences, Benue State University, Makurdi. The drug was administered orally via gavage after dissolving in distilled water.

2.3 Preparation of Activated Charcoal

Activated charcoal was derived from wood charcoal collected from a domestic kitchen in Otukpa, Ogbadibo Local Government Area, Benue State. The charcoal was thoroughly rinsed with water to remove debris, dried, and ground into fine powder. To activate the charcoal, 1.6 g of the powdered charcoal was soaked in a solution of 64 g of calcium chloride dissolved in water for 24 hours. Afterward, the mixture was filtered, and the charcoal

was subjected to thermal activation by heating over a gas flame until fully dried. The activated charcoal was then sieved to obtain fine particles, which were stored in airtight containers for use in the experiment.

2.4 Housing and Feeding Conditions

The rats were housed in five (5) plastic cages, ensuring adequate space for movement. Vital animal feed was purchased from a feed store in Wurukum, Makurdi, and stored at an optimal temperature in the animal house to maintain freshness.

2.5 Experimental Design

The study was conducted over 14 days following the acclimatization period. The 25 Wistar rats were divided into five (5) experimental groups, each consisting of five (5) rats, and were treated as follows:

- **Group I (Control Group):** Received 5 ml/kg body weight of normal saline orally at 12-hour intervals for 14 days.
- **Group II:** Received 200 mg/kg body weight of Lincomycin orally at 12-hour intervals for 14 days.
- **Group III:** Received a diet consisting of 75% standard feed mixed with 25% activated charcoal, along with water and 200 mg/kg of Lincomycin, administered at 12-hour intervals for 14 days.
- **Group IV:** Received a diet consisting of 50% standard feed mixed with 50% activated charcoal, along with water and 200 mg/kg of Lincomycin, administered at 12-hour intervals for 14 days.
- **Group V:** Received a diet consisting of 25% standard feed mixed with 75% activated charcoal, along with water and 200 mg/kg of Lincomycin, administered at 12-hour intervals for 14 days.

2.6 Animal Sacrifice and Sample Collection

At the end of the 14-day experimental period, the animals were humanely sacrificed using chloroform anesthesia. Blood samples were collected via cardiac puncture using sterile disposable syringes and stored in EDTA bottles for biochemical analysis. The kidneys were excised and fixed in 10% formal saline for histological examination and tissue processing.

2.7 Biochemical Analyses

2.7.1 Creatinine Determination

Serum creatinine levels were measured using the modified Jaffe method with the Quimica Clinica Applicada (QCA) creatinine test kit. In this method, creatinine in an alkaline solution reacts with picrate to form a colored complex. The rate of absorbance increase at 546 nm was measured and was directly proportional to the creatinine concentration, expressed in mg/dL.

2.7.2 Urea Determination

Serum urea concentration was estimated using the modified Searcy method with the Quimica Clinica Applicada (QCA) enzymatic urea test kit (Diamond Diagnostic, Hanover, Germany). The urea concentration was expressed in mg/dL.

2.7.3 Estimation of Lipid Peroxidation (Malondialdehyde, MDA)

Lipid peroxidation in renal tissues was assessed colorimetrically using the thiobarbituric acid reactive substances (TBARS) method of Buege and Aust (1978). A principal component of TBARS, malondialdehyde (MDA), is a marker of lipid peroxidation. Briefly, 0.1 mL of tissue homogenate in Tris-HCl buffer (pH 7.5) was mixed with 2 mL of a 1:1:1 solution of thiobarbituric acid (0.37%), trichloroacetic acid (15%), and hydrochloric acid (0.25 N). The mixture was incubated in a water bath at 95°C for 15 minutes, cooled, and centrifuged. The absorbance of the supernatant was measured at 535 nm against a blank. MDA concentration was calculated using its molar absorptivity (1.56 x 105 M-1cm-1) and expressed as nmol/mg protein.

2.7.4 Superoxide Dismutase (SOD) Activity Assay

Superoxide dismutase (SOD) activity was measured following the method of Winterbourn (1975), as described by Rukmini *et al*. (2004). This assay is based on the ability of SOD to inhibit the reduction of nitro-blue tetrazolium (NBT). The reaction mixture contained 2.7 mL of 0.067M phosphate buffer (pH 7.8), 0.05 mL of 0.12mM riboflavin, 0.1 mL of 1.5mM NBT, 0.05 mL of 0.01M methionine, and 0.1 mL of enzyme extract. The tubes were uniformly illuminated in an aluminum foil-lined box with a 15W fluorescent lamp for 10 minutes. A control reaction lacking the enzyme extract was also included. The absorbance was measured at 560 nm. One unit of SOD activity was defined as the amount of enzyme required to inhibit NBT reduction by 50%. Results were expressed as units/mg protein.

2.7.5 Histological Tissue Processing

Kidney tissues were embedded in molten paraffin wax and allowed to solidify in metallic tissue molds. The

blocks were then cooled at 5°C for 15 minutes, removed from the molds, and trimmed. Serial sections (3 µm thick) were obtained using a rotary microtome and floated in a water bath at 55°C. The sections were mounted onto clean frosted-end slides, placed on a hot plate for 40 minutes for proper adhesion, and then deparaffinized, hydrated, air-dried, and stored for staining.

2.7.6 Haematoxylin and Eosin (H&E) Staining

1) Sections were dewaxed in xylene (3 changes, 5 min each).
2) Rehydration was performed through descending ethanol concentrations (absolute, 95%, 80%, and 70%).
3) Staining was carried out using Harris hematoxylin (5 min).
4) Sections were rinsed in running tap water to remove excess stain.
5) Differentiation was performed in 1% acid alcohol (3 sec).
6) Sections were blued in running tap water (10 min).
7) Counterstaining with 1% eosin was done (1 min).
8) Dehydration was achieved through ascending ethanol concentrations (70%, 80%, 95%, and absolute).
9) Sections were cleared in xylene, air-dried, and mounted with dibutyl phthalate polystyrene xylene (DPX).

Slides were examined under a light microscope, and photomicrographs were captured.

2.8 Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23. Mean values were compared using one-way analysis of variance (ANOVA), and intergroup comparisons were performed using the least significant difference (LSD) post-hoc test. A p-value of <0.05 was considered statistically significant.

2.9 Ethical Considerations

This study was conducted in compliance with the ethical guidelines of the Ethical Committee of the College of Health Sciences, Benue State University, Makurdi. Approval was obtained before the commencement of the research.

3. Results

3.1 Body Weight Changes

The results of the body weight changes across the different groups show a significant variation in weight differences as presented in Figure 1. Group I (Control) had a mean weight increase of 22.10±10.81 g, while Group II (Negative Control: Lincomycin) showed a significantly higher weight increase of 38.26±17.98 g (P=.03 compared to Control), indicating a positive effect of Lincomycin on body weight gain. Group III, with a 75% feed and 25% activated charcoal (AC) mix, showed a moderate weight gain of 23.62±13.86 g, which was not significantly different from the control. Group IV, with a 50% feed and 50% AC mix, had a smaller weight increase of 14.82±6.51 g (P=.02 compared to the Negative Control), suggesting a potential inhibitory effect of the higher AC content. Group V (25% feed + 75% AC) showed a weight decrease of -8.56±6.74 g ($P<0.05$ compared to both Control and Negative Control), highlighting a significant negative impact of higher AC content on body weight.

The results suggest that while Lincomycin enhances body weight, the inclusion of activated charcoal, particularly in high amounts, negatively affects body weight gain.

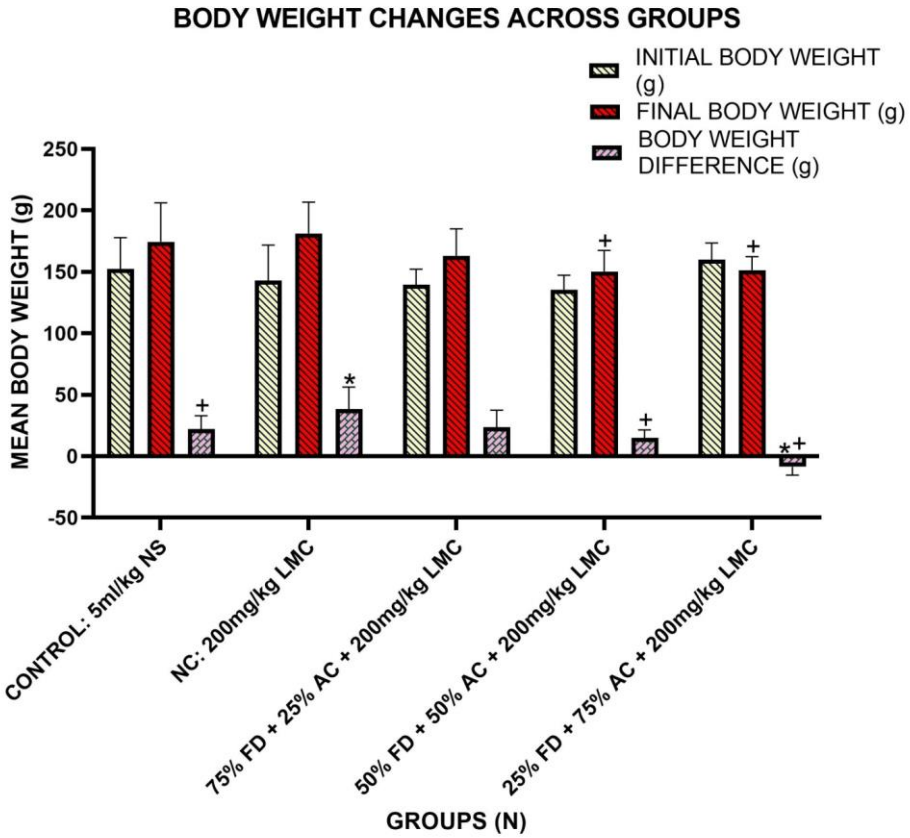

Figure 1. Simple Bar Chart Showing the Mean Body Weight Changes across Groups

N = 5; NC = Negative Control; LMC = Lincomycin; AC = Activated Charcoal; FD = Feed; *P<0.05 Compared to the Control Group; +P<0.05 Compared to the Negative Control Group.

3.2 Kidney Weight

The results presented in Figure 2 show the mean kidney weight and kidney/body weight ratio across groups. The kidney weight was consistent across all groups, with a mean of 1.70±1.30 g. However, the kidney/body weight ratio showed notable variation, particularly in Group V (25% Feed + 75% Activated Charcoal + 200 mg/kg Lincomycin), which had a significantly lower ratio of -0.84±1.49, compared to both the control and negative control groups (P=.01).

This suggests that the combination of activated charcoal and Lincomycin at this specific dosage and feed ratio might have a pronounced impact on kidney function or morphology, potentially altering the kidney's relative mass in relation to body weight. No significant differences were observed in kidney weight among all groups, indicating that the variations in the kidney/body weight ratio may reflect physiological changes induced by the treatments, particularly in Group V.

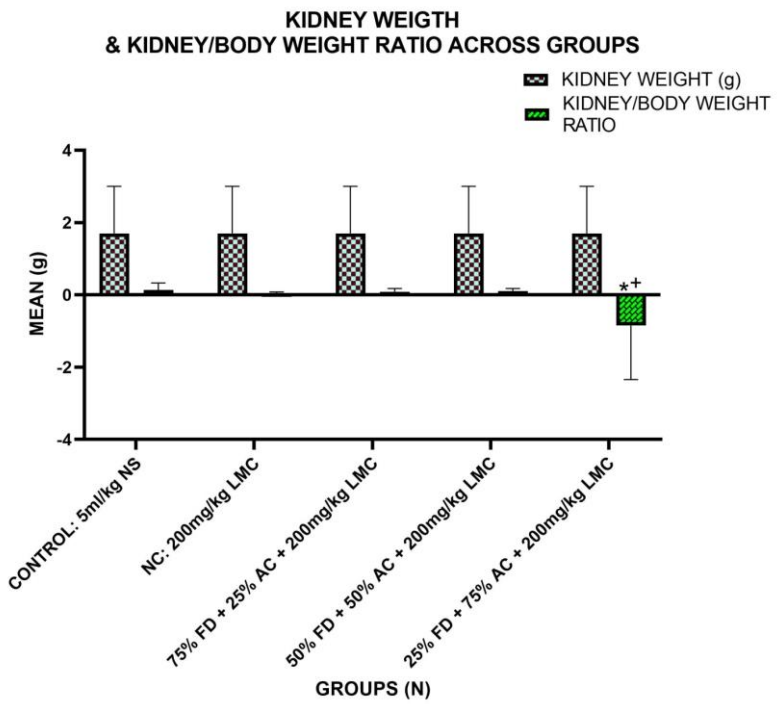

Figure 2. Simple Bar Chart Showing the Mean Body Weight & Body/Kidney Weight Ratio across Groups

N = 5; NC = Negative Control; LMC = Lincomycin; AC = Activated Charcoal; FD = Feed; *P<0.05 Compared to the Control Group; +P<0.05 Compared to the Negative Control Group.

3.3 Kidney Function Parameters

The results presented in Figure 3 show the mean kidney function parameters (creatinine and urea levels) across groups. Group I (Control) showed a creatinine level of 0.85±0.04 mg/dl and urea level of 25.78±1.19 mg/dl. Group II (Negative Control, 200 mg/kg LMC) showed a significant decrease in both creatine (0.59±0.07 mg/dl) and urea (19.85±2.11 mg/dl) compared to the Control group (P<0.05), suggesting a potential reduction in kidney function following Lincomycin (LMC) administration. Groups III, IV, and V, which received varying proportions of feed and activated charcoal with 200mg/kg LMC, showed a range of creatinine levels (0.86±0.05 to 0.96±0.12 mg/dl) and urea levels (21.33±1.90 to 21.65±2.40 mg/dl), but these differences were not statistically significant compared to the Control.

This suggests that activated charcoal mitigate the effects of lincomycin on kidney function, as indicated by the absence of significant elevation in creatinine and urea levels. The findings suggest that lincomycin alone impairs kidney function, but activated charcoal offers protective effects.

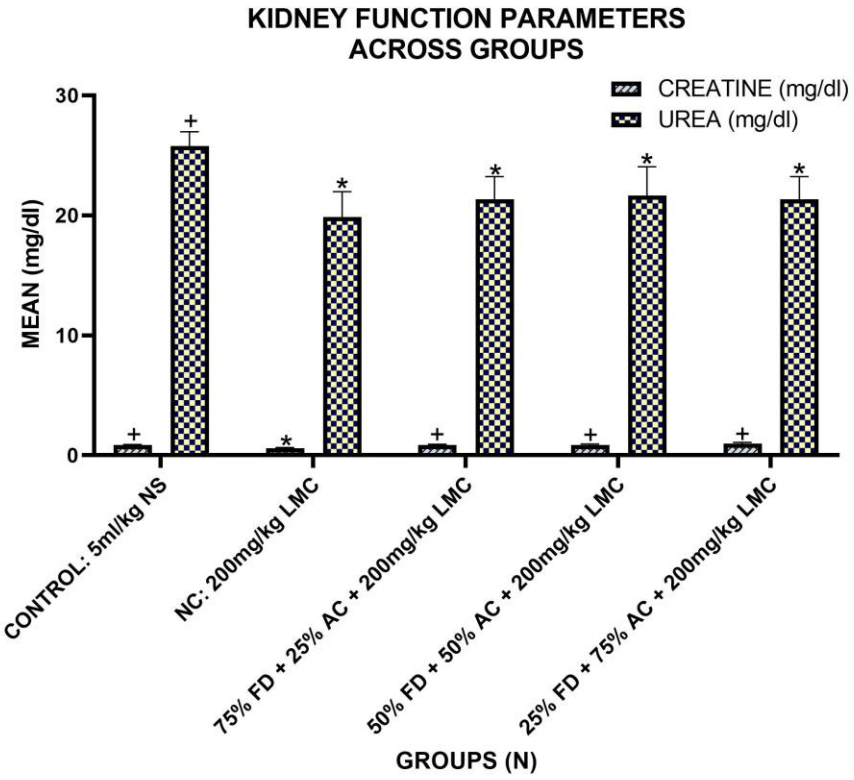

Figure 3. Simple Bar Chart Showing the Mean Kidney Function Parameters across Groups

N = 5; NC = Negative Control; LMC = Lincomycin; AC = Activated Charcoal; FD = Feed; *P<0.05 Compared to the Control Group; +P<0.05 Compared to the Negative Control Group.

3.4 Oxidative Stress

The results in Figure 4 show the mean oxidative stress markers, Superoxide Dismutase (SOD) and Malondialdehyde (MDA), across groups. Group I, the control group, showed the highest SOD levels (28.89±2.23 U/mg protein) and the lowest MDA levels (0.65±0.12 nmol/mg protein). Group II, the negative control group treated with Lincomycin (LMC), had significantly lower SOD levels (14.25±1.81 U/mg protein) and significantly higher MDA levels (3.08±0.10 nmol/mg protein) compared to the control group, indicating increased oxidative stress.

Groups III, IV, and V, which received varying combinations of feed and activated charcoal (AC) along with LMC, showed improvements in oxidative stress markers compared to the negative control. Group III (75% feed + 25% AC) had moderately improved SOD (18.92±3.02 U/mg protein) and reduced MDA (1.67±0.54 nmol/mg protein). Group IV (50% feed + 50% AC) showed a further increase in SOD (22.37±2.77 U/mg protein) and a significant reduction in MDA (0.82±0.49 nmol/mg protein), while Group V (25% feed + 75% AC) had the highest SOD levels (25.40±5.31 U/mg protein) and a moderate reduction in MDA (1.02±0.71 nmol/mg protein). Statistical analysis indicated significant differences (P<0.05) in SOD and MDA levels between the control and experimental groups, as well as between the negative control and other experimental groups. These results suggest that activated charcoal helps to mitigate oxidative stress induced by LMC, with greater efficacy observed at higher doses of activated charcoal.

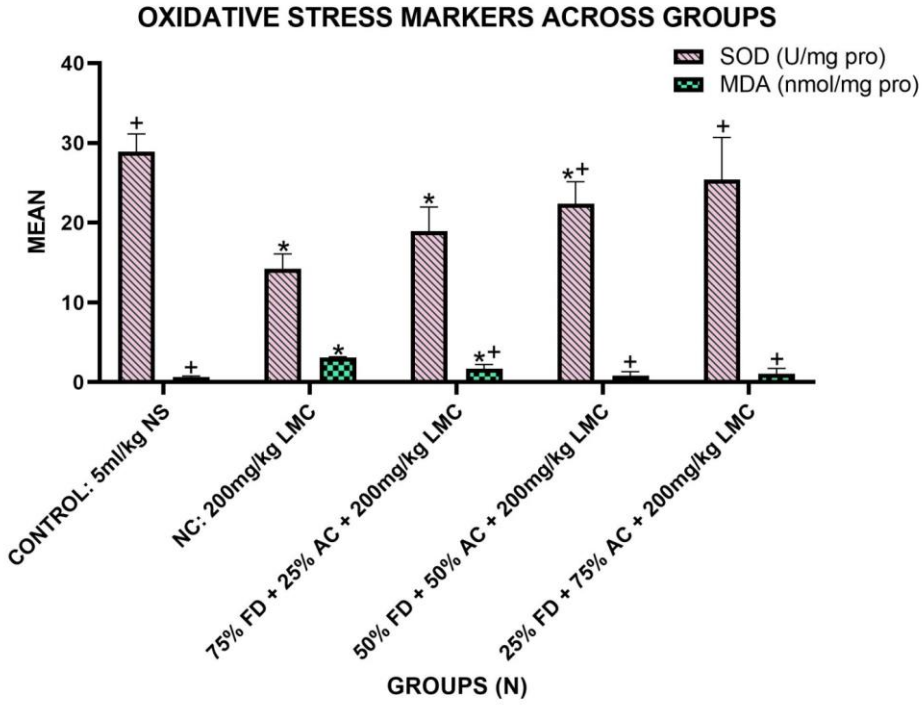

Figure 4. Simple Bar Chart Showing the Mean Oxidative Stress Markers across Groups

N = 5; NC = Negative Control; LMC = Lincomycin; AC = Activated Charcoal; FD = Feed; *P<0.05 Compared to the Control Group; +P<0.05 Compared to the Negative Control Group.

3.5 Histological Analysis

Histological examination of the kidney tissue in Group I (control) revealed normal renal architecture. The glomeruli were well-defined, showing a spherical structure composed of simple endothelial cell-lined capillaries. The Bowman's capsule appeared intact with a well-demarcated, round structure lined by simple squamous epithelium. The proximal convoluted tubules displayed cuboidal epithelial cells with prominent microvilli, while the distal convoluted tubules consisted of rounded cuboidal epithelial cells lacking microvilli. The renal medulla contained the loop of Henle, which was lined by simple squamous epithelium.

In contrast, the renal tissue of Groups II–IV showed varying degrees of histopathological alterations. The glomerular endothelial cells exhibited degenerative changes, with evidence of desquamation and structural disruption. The Bowman's capsule showed signs of necrosis, with thinning and irregularity of its lining, leading to an expanded and more tenuous Bowman's space. In Group V, the proximal tubular epithelial cells displayed significant necrosis, characterized by desquamation of the cuboidal epithelium, cytoplasmic degeneration, and nuclear loss. Inflammatory cell infiltration was observed within the proximal tubules, with numerous dark-staining, round inflammatory cells surrounding the damaged tubular epithelium. The severity of these degenerative changes was most pronounced in Group II, while Groups III and IV exhibited comparatively less severe but still notable structural distortions.

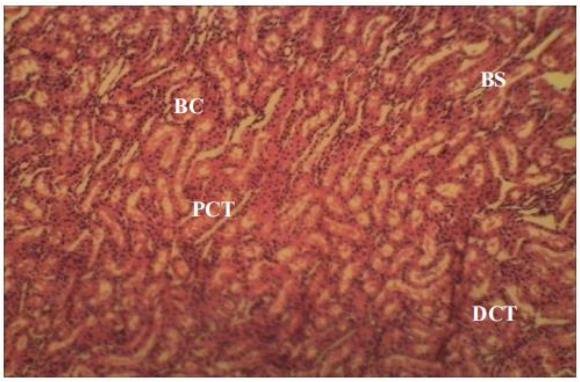

Plate 1: Photomicrograph of Kidney Section from Group I showing Bowman's Capsule (BC), Bowman's Space (BS), Proximal (PCT), & Distal Convoluted Tubule (DCT) (H&E x40)

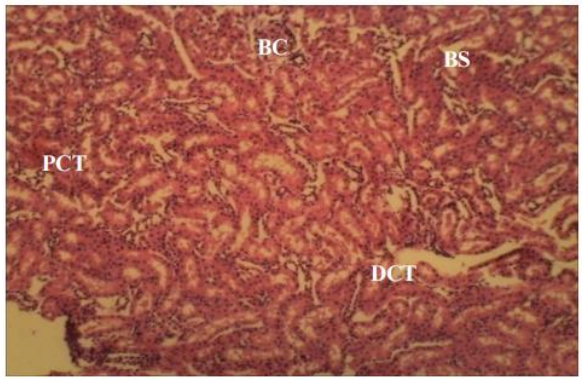

Plate 2: Photomicrograph of Kidney Section from Group II showing Bowman's Capsule (BC), Bowman's Space (BS), Proximal (PCT), & Distal Convoluted Tubule (DCT) (H&E x40)

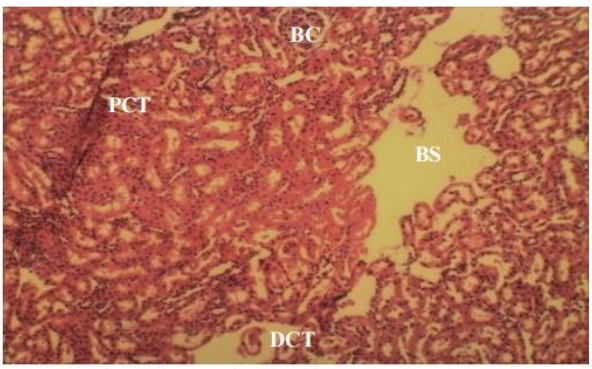

Plate 3: Photomicrograph of Kidney Section from Group III showing Bowman's Capsule (BC), Bowman's Space (BS), Proximal (PCT), & Distal Convoluted Tubule (DCT) (H&E x40)

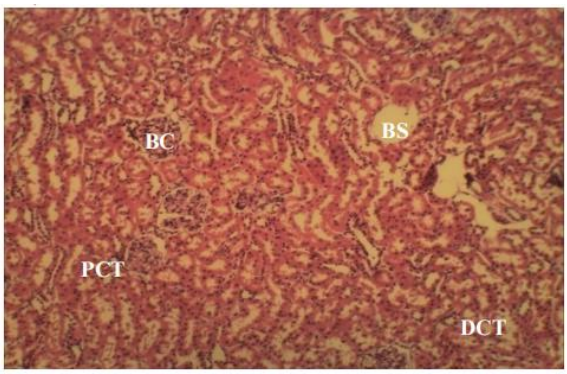

Plate 4: Photomicrograph of Kidney Section from Group IV showing Bowman's Capsule (BC), Bowman's Space (BS), Proximal (PCT), & Distal Convoluted Tubule (DCT) (H&E x40)

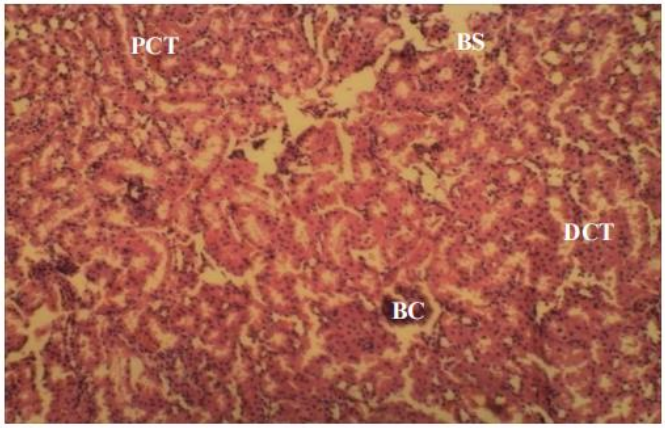

Plate 5: Photomicrograph of Kidney Section from Group V showing Bowman's Capsule (BC), Bowman's Space (BS), Proximal (PCT), & Distal Convoluted Tubule (DCT) (H&E x40)

4. Discussion

The results from this study on the effects of Lincomycin (LMC) administration and activated charcoal (AC) supplementation provide insightful evidence of the complex interactions between these treatments. The findings reveal the impact of LMC on weight gain, kidney morphology, and kidney function, alongside the therapeutic potential of activated charcoal in mitigating the adverse effects of LMC-induced nephrotoxicity.

The body weight changes observed in this study suggest that Lincomycin (LMC) has a significant impact on

weight gain, as evidenced by the significant increase in body weight in Group II (Negative Control, 200 mg/kg LMC) compared to the control group (Group I). This result aligns with previous studies reporting the weight-enhancing effects of LMC in animal models, likely due to its antimicrobial activity and its impact on metabolic processes (Sahraei *et al*., 2020). Lincomycin may induce an increase in body weight by promoting retention of fluids or modulating metabolic pathways, which is observed in the significant weight increase in Group II. In contrast, the inclusion of activated charcoal (AC), particularly in higher amounts, showed a dose-dependent negative impact on body weight. Group V (25% feed + 75% AC) exhibited a significant weight decrease, indicating that the higher content of AC may have a detrimental effect on weight gain. This finding is consistent with the potential gastrointestinal adsorptive properties of activated charcoal, which could bind to nutrients and reduce their bioavailability, thereby impeding weight gain (Nakamura *et al*., 2023).

The lack of significant difference in body weight between Group I and Groups III and IV suggests that moderate amounts of activated charcoal (up to 50% feed) do not substantially impair weight gain, and may indicate a balance in therapeutic efficacy without major adverse metabolic effects. These findings are in line with prior studies that have reported mild adverse effects on body weight with higher AC concentrations (Zhang *et al*., 2021).

The results concerning kidney weight show no significant differences across the groups, suggesting that the absolute kidney mass were not directly impacted by LMC administration or AC supplementation. However, the kidney/body weight ratio showed significant variation, particularly in Group V, which had a notably lower ratio compared to both the control and negative control groups. This suggests that the combination of LMC and a high dose of AC (75%) could potentially alter kidney morphology or induce structural changes that affect the kidney's relative size to body weight.

The observed decrease in kidney/body weight ratio in Group V could indicate that higher doses of activated charcoal may induce physiological changes in renal structure or function, possibly due to altered hemodynamics or drug absorption (Zhang *et al*., 2022). However, since kidney weight itself did not significantly vary, this change may be attributed to the interplay between renal function and the physiological effects of LMC and activated charcoal, rather than a direct impact on kidney mass.

The findings from kidney function parameters, specifically serum creatinine and urea levels, show a clear impact of LMC on kidney function. Group II (Negative Control) exhibited significant reductions in both creatinine and urea levels, suggesting that LMC administration could reduce kidney function. This is consistent with previous studies that have reported nephrotoxic effects of LMC, including alterations in renal filtration capacity (Adetunji *et al*., 2021). The reduction in kidney function as indicated by lower creatinine and urea levels in Group II could reflect acute kidney injury (AKI) induced by LMC.

The groups receiving varying doses of activated charcoal (Groups III, IV, and V) showed no significant changes in creatinine or urea levels compared to the control group. This absence of significant elevation in kidney function markers suggests that activated charcoal may exert a protective effect against the renal toxicity induced by LMC. Activated charcoal is known for its ability to absorb toxins in the gastrointestinal tract, thus reducing systemic absorption of harmful substances like LMC (Sahraei *et al*., 2021). This protective effect could explain why activated charcoal supplementation, even at high doses (as in Group V), did not significantly exacerbate kidney dysfunction despite the presence of Lincomycin. These results corroborate findings from other studies that have demonstrated the protective role of activated charcoal in mitigating nephrotoxicity through the reduction of toxin absorption (Liang *et al*., 2022; Nakamura *et al*., 2023).

Recent studies have examined the nephrotoxic effects of various antibiotics, including Lincomycin, and the potential mitigating effects of activated charcoal. For example, Adetunji *et al*. (2021) reported that LMC administration in rats resulted in significant renal dysfunction, which aligns with the findings of impaired kidney function, as indicated by reduced creatinine and urea levels in the current study. Furthermore, their study demonstrated that activated charcoal supplementation improved renal function; supporting findings of this study that activated charcoal offers protective effects against LMC-induced nephrotoxicity.

Additionally, Liang *et al*. (2022) explored the gastrointestinal adsorptive properties of activated charcoal and its role in reducing systemic absorption of nephrotoxic drugs. Their results, which suggest that activated charcoal effectively reduces the severity of renal damage in the presence of toxic substances, are consistent with the observations that activated charcoal mitigated the kidney damage induced by Lincomycin in the current study.

Similarly, Nakamura *et al*. (2023) studied the effects of activated charcoal in a model of drug-induced nephropathy and found that charcoal supplementation reduced serum creatinine and urea levels, corroborating the findings of the beneficial effects of activated charcoal on kidney function in this research.

Oxidative stress is a critical factor in the pathogenesis of nephrotoxicity, and the results of this study clearly demonstrate the impact of LMC-induced oxidative stress on renal function. The control group (Group I) showed

the highest levels of SOD, an important antioxidant enzyme that mitigates oxidative damage by converting superoxide radicals into hydrogen peroxide, and the lowest MDA levels, a marker of lipid peroxidation. These findings reflect a healthy balance between oxidative and antioxidative processes. In contrast, Group II, which received LMC without activated charcoal, showed significantly lower SOD levels and higher MDA levels. This suggests that LMC induces oxidative stress in the kidneys, which can contribute to nephrotoxicity by promoting lipid peroxidation and oxidative damage to renal tissues.

The protective effects of activated charcoal were evident in Groups III, IV, and V, where varying doses of AC were administered alongside LMC. Group III (75% feed + 25% AC) showed a moderate improvement in oxidative stress markers, with an increase in SOD and a reduction in MDA compared to the negative control. A more pronounced effect was observed in Group IV (50% feed + 50% AC), which exhibited a significant increase in SOD and a marked reduction in MDA. Group V (25% feed + 75% AC) showed the highest SOD levels and the lowest MDA levels, highlighting the dose-dependent therapeutic potential of activated charcoal in mitigating oxidative stress. These results align with previous research that demonstrates the antioxidant properties of activated charcoal, which can adsorb toxins and free radicals, thereby preventing or reducing oxidative damage (Wang *et al*., 2021; Jung *et al*., 2020).

The observed improvements in oxidative stress markers (SOD and MDA) following AC treatment suggest that AC plays a significant role in modulating the redox status of the kidney, reducing the burden of oxidative stress induced by LMC. The higher efficacy at higher doses of activated charcoal (as seen in Group V) could be attributed to the increased adsorptive capacity of AC, which may facilitate more effective clearance of toxins and free radicals from the systemic circulation, thereby providing a protective effect on renal tissue.

The histological findings further support the oxidative stress data. In Group I (control), the kidney tissue appeared normal, with well-preserved glomerular and tubular structures, indicating healthy renal function. However, in Group II (negative control), which received LMC, histological alterations such as glomerular endothelial degeneration, Bowman's capsule necrosis, and tubular cell damage were evident. These changes are consistent with previous studies that have demonstrated renal histopathological alterations in response to LMC administration, suggesting that LMC induces nephrotoxic effects by damaging glomerular and tubular structures (Chrysafides *et al*., 2021; Yu *et al*., 2023).

In the experimental groups (Groups III, IV, and V), the extent of histological damage was reduced compared to Group II, with Group V showing the least severe alterations. While Group V exhibited more pronounced necrosis in proximal tubular epithelial cells, the inflammatory cell infiltration was less extensive compared to Group II, indicating a degree of protection afforded by activated charcoal. This finding supports the notion that activated charcoal can ameliorate LMC-induced renal damage, possibly by adsorbing circulating toxins and reducing the inflammatory response (Ng *et al*., 2021).

Similar studies have explored the role of activated charcoal in mitigating oxidative stress and nephrotoxicity, providing insight into the underlying mechanisms of its protective effects. Jung *et al*. (2020) reported that activated charcoal, through its adsorptive properties, can reduce oxidative stress and alleviate kidney injury in animal models of nephrotoxicity. Similarly, Wang *et al*. (2021) found that activated charcoal administration significantly reduced MDA levels and increased antioxidant enzyme activities in rat models of renal damage. These findings are consistent with the results of the present study, which also demonstrate that activated charcoal can alleviate oxidative stress markers in LMC-induced nephrotoxicity.

In a study by Chrysafides *et al*. (2021), activated charcoal was shown to reduce renal histopathological damage in rats exposed to nephrotoxic agents, similar to the protection observed in Groups III-V of the current study. Moreover, Yu *et al*. (2023) reported that higher doses of activated charcoal provide greater protective effects against oxidative damage, which is in line with the dose-dependent efficacy observed in this study, particularly in Group V.

5. Conclusion

This study demonstrates that Lincomycin (LMC) induces nephrotoxicity, as evidenced by alterations in kidney function, oxidative stress markers, and histopathological changes. Activated charcoal (AC) supplementation showed a protective effect against LMC-induced renal damage, with a dose-dependent improvement in oxidative stress markers and kidney function. Higher doses of AC, particularly in Group V, effectively reduced oxidative stress and renal tissue damage. These findings highlight the potential of activated charcoal as a therapeutic agent for mitigating LMC-induced nephrotoxicity, supporting its role in protecting renal function through the adsorption of toxins and free radicals.

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Transmission, Diagnosis, and Treatment of Acute and Chronic Hepatitis E

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Abstract

Hepatitis is the liver inflammatory disease that is caused by chemicals, drugs, or by the infection with different kinds of viruses. Hepatitis E infection is a disease that affects the liver and is caused by hepatitis E virus (HEV), a virus that can infect both animals and humans. The HEV infection can cause acute liver failure, chronic hepatitis, and liver cirrhosis that remain a clinical challenge and still account for high mortality. It is the main cause of enterically transmitted hepatitis in humans worldwide. Among weakened immune patients it can lead to chronic hepatitis that may result a life-threatening illness, such as fulminant liver failure. There are eight genotypes: HEV 1-8; and genotypes 1 and 2 infect humans exclusively. The virus is transmitted mainly through the fecal-oral route of contaminated food and water. Active screening, reducing misdiagnosis, improving patient management, proper medications, supportive treatments, and timely antiviral therapy for severe and chronic cases are important measures to reduce the morbidity and mortality due to hepatitis E. This study focuses on the transmission, management, and treatment of HEV infection.

Keywords: HEV, acute and chronic hepatitis, screening, antiviral therapy, ribavirin, pregnancy

1. Introduction

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis globally that is responsible for the major liver infection and may develop in people who have a suppressed immune system. Hepatitis E occurs as both sporadic and epidemic outbreaks of acute hepatitis in developing countries, leading to a self-limiting disease (Pilot et al., 1987). In most cases HEV (where E for epidemic) infections are mild or asymptomatic, but in some cases slightly symptomatic and the disease is rarely fatal (Kamar et al., 2012). Infection with the HEV may be related to acute illness, chronic hepatitis, liver cirrhosis, and liver failure (Guerra et al., 2017). The HEV also shows extrahepatic manifestations, such as pancreatitis, neurological symptoms, renal injury, hematological disorders, glomerulonephritis, and mixed cryoglobulinemia (Nimgaonkar et al., 2018). It affects more men than women, with a ratio of 2:1 in developing countries and more than 3:1 in developed countries (Kamar et al., 2014).

The first well-documented epidemic acute hepatitis named non-A, non-B viral hepatitis was occurred in 1955 in New Delhi, India that was affected 29,000 people, which occurred due to fecal contamination of drinking water (Wong et al., 1980). Hepatitis E was first identified by Indian physician Mohammad Sultan Khuroo as non-A, non-B viral hepatitis during an epidemic of hepatitis, which occurred in Kashmir Valley, India in 1978 that affected over 50,000 inhabitants of which almost 1,700 died (Kumar et al., 2013). In 1983, the Russian virologist Mikhail Surenovich Balayan visualized the virus through electron microscopy when examining his own feces after self-administration of contaminated material (Meng, 2011; Mikhailov et al., 2021). The HEV was discovered in 1983 by Russian virologists investigating an outbreak of unexplained hepatitis using immunoelectron microscopy among Soviet soldiers serving in Afghanistan. In 1989, the viral genome was

successfully sequenced and this pathogen was formally designated as HEV (Izopet et al., 2014). In 1991, American virologist Albert W. Tam and his team have succeeded in cloning and sequencing the genome of the virus and it is named “hepatitis E virus (HEV)” (Tam et al., 1991).

Hepatitis E is water-borne disease that spreads by the HEV contamination with the fecal material ingestion. The HEV infection may prove to be dangerous in pregnant women, especially during the third trimester; older people; and people who have existing chronic liver disease (Polley et al., 2022). In severe stage, the disease is associated with a clinical syndrome called fulminant liver failure, with death rates about 20% (Ali, 2018). Sometimes for adverse effects on the mother may happen, such as preterm delivery, abortion, low birth weight, stillbirth, and neonatal death (Patra et al., 2007). The prevalence is highest in East and South Asia. Also, Bangladesh, India, China, Middle-East, Mediterranean region, Ethiopia, Mexico, South America, and Kenya carry the highest burdens of HEV infection (Zeng et al., 2021).

From 1990 to 2019, the incidence rates of HAV, HCV, and HEV infection have remained stable (Zeng et al., 2021). Every year there are an estimated 20 million HEV infections globally with 3.3 million symptomatic cases, 3000 stillbirths, and 44,000–70,000 HEV-related deaths per year (WHO, 2020). The HEV seroprevalence is high in developing countries, such as in India and Southeast Asia, ranging from 27% to 80% (Guerra et al., 2017).

2. Literature Review

In any type of research, literature review is an introductory area, where works of previous researchers are included (Polit & Hungler, 2013). It deals with secondary research sources and does not think about coming research work (Gibbs, 2008). Silvia E. Tritz and her coauthors have investigated zoonotic transmission of HEV in rural settings of Lao People’s Democratic Republic where humans are in close contacts with ruminants and where pigs are rare. They have highlighted on the need to raise the awareness of the rural population about water- and food- borne pathogens, and about the role of cattle as a possible source of infection (Tritz et al., 2018).

Chia-Yu Chiu and his coauthors have studied the cancer patients with HEV infection. They have observed that cancer patients with hematologic malignancies may be at risk for HEV viremia and chronic infection refractory to antiviral treatment (Chiu et al., 2022). Qiumin Luo and her coworkers have focused on the clinical presentation, management, and prevention of hepatitis E to reduce worldwide morbidity and mortality (Luo et al., 2024). Danielle M. Yugo and Xiang-Jin Meng have studied the current understanding of HEV transmission routes with emphasis on food and environmental sources and the prevalence of HEV in animal species with zoonotic potential in humans (Yugo & Meng, 2013).

Chunchen Wu and her coworkers have shown that the HEV causes self-limiting viral hepatitis, and among pregnant women the infection can be severe that has been associated with up to 30% mortality in the third trimester. They have also indicated that in pregnancy HEV is also associated with high rates of preterm labor and vertical transmission. They have summarized the current knowledge about HEV infection during pregnancy that focuses on the epidemiology, clinical manifestations, and mechanisms underlying severe liver injury; and also management and prevention of HEV infection during pregnancy (Wu et al., 2020).

Toni L. Meister and her coauthors have described various approaches to cultivate HEV in cellular and animal models, and have indicated how these systems are used to study HEV infections and evaluate anti-HEV drug candidates (Meister et al., 2019). Subrat Kumar and his coworkers have reviewed the currently available information with regard to the molecular biology, pathobiology, and epidemiology of HEV infection. They have also reviewed the current therapeutic interventions and strategies being used to control HEV infection, with emphasis on possible approaches that could be used to develop an effective vaccine against HEV (Kumar et al., 2013).

3. Research Methodology of the Study

All academicians take the research as a challenging work to lead in academic world (Pandey & Pandey, 2015). A well-built outline of the study and an efficient understanding are crucial to reach the goal of a research (Tie et al., 2019). Methodology is a guideline to perform good research that helps the researchers to increase the trust of a reader in the research findings (Kothari, 2008). Research methodology is the science and philosophy behind all researches that provide the principles for organizing, planning, designing and conducting good research (Legesse, 2014).

To prepare this article we have used secondary data that are collected from both published and unpublished data sources (Mohajan, 2024a-j; Mohajan & Mohajan, 2023a-d). The published data are collected from various sources, such as websites, national and international journals and e-journals, books and handbooks of famous authors, internet, etc. (Mohajan, 2017, 2018, 2020).

4. Objective of the Study

Main objective of this article is to discuss the infectious disease that is associated by hepatitis E virus (HEV), which is responsible for the major liver damage. The HEV is related to acute illness and also chronic hepatitis. It can be transmitted via the fecal-oral route, zoonotic route, and blood transfusion route. Common symptoms of it are jaundice, fever, tiredness, loss of appetite, etc. The disease is self-limiting and treatment is palliative and supportive. Other minor objectives of the study are as follows:

1) to focus on the virology of HEV,

2) to highlight on the symptoms and transmission of HEV, and

3) to indicate the diagnosis and treatment of HEV.

5. Virology of HEV

The HEV is a small, icosahedral, non-enveloped, single-stranded, positive-sense RNA virus with genome of 7.2 kb and 27-34nm in diameter that is highly unstable due to the lack of a lipid membrane (Mayr et al., 2018). It consists of short 5′ non-translated region (NTR) with 7-methylguanylate cap, 27-35 nucleotides in length and the 3′ non-translated region (NTR) is 65-74 nucleotides in length, terminated with a poly end with 150-200 nucleotides in length. The 3′ end of the chain is polyadenylated and the 5′ end is structurally characterized by the capping (Vasickova et al., 2007). It contains three open reading frames (ORF): ORF1, ORF2 and ORF3 (Figure 1). The ORF1 is the largest, containing several conserved domains, and encodes non-structural proteins that is about 1693 amino acids long with at least four putative functional domains (Kenney & Meng, 2019), the ORF2 encodes the viral 660 amino acids capsid protein that has been divided into three domains (Yin et al., 2018), and the ORF3 encodes a 113 or 114 amino acids phosphoprotein, depending on the genotype (Ding et al., 2017).

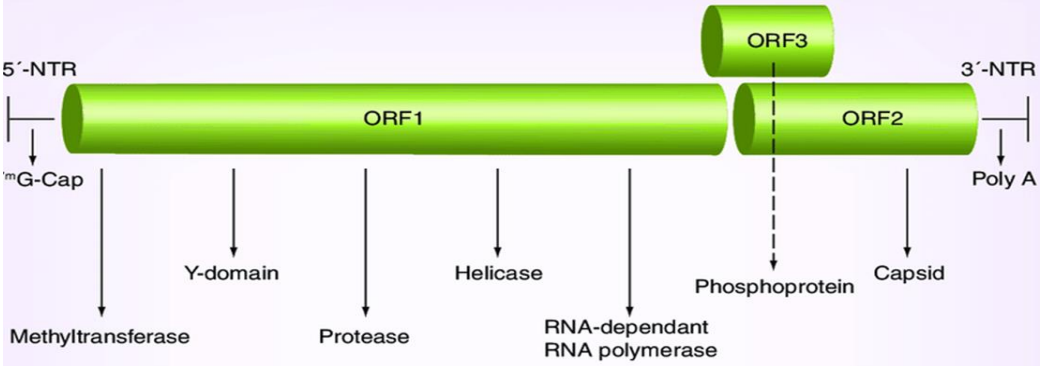

Figure 1. Genomic structure of the HEV. Source: Olyaee et al. (2009).

The HEV replicates in the cytoplasm of cells and also can replicate in hepatocytes, small intestine and colon cells, and lymph nodes (Kamar et al., 2014). It is classified into the family Hepeviridae, which is divided in two genera, Orthohepevirus and Piscihepevirus. The genus Orthohepevirus encompasses all mammalian and avian HEV variants, and is subdivided into four species: A-D (Pérez-Gracia et al., 2017).

At present HEV can be clustered genetically into 8 genotypes (GTs); HEV 1-8 that recognize with distinct differences in geographic distribution (Sridhar et al., 2017). It is classified into different subtypes, such as 1a-e, 2a-b, 3a-j, and 4a-g (Meng et al., 1999). The GTs 1 and 2 are endemic and restricted to humans, and are associated with large outbreaks through the fecal-oral route with contaminated water. The GT1 can be classified into 5 subtypes, such as 1a-e that have been isolated from tropical and several subtropical countries in India, Nepal, China, and North Africa (Song, 2010). The GT2 can be classified into 2 subtypes, such as 2a-b that have been isolated from Mexico, Nigeria, and Chad (Pelosi & Clarke, 2008). These are often associated with epidemics in developing countries due to poor hygiene and sanitation (Nimgaonkar et al., 2018).

The GTs 3 and 4 are zoonotic and have been detected in various mammalian species (swine viruses) worldwide and occasionally infect humans (as accidental hosts) that are autochthonous in several industrialized countries (Shrestha et al., 2015). These are associated with food-borne transmission, linked to the consumption of raw or undercooked infected meat from wild animals, such as deer and boar, and other game meats; watery non-mammals, such as shellfish and crabs; and domestic animals, such as pig and rabbit (Guerrant et al., 2011). These are prevalent in industrialized countries and are associated with sporadic and clustered cases of hepatitis E in these regions (Khuroo et al., 2016). The GT3 can be classified into 10 subtypes, such as 3a-j and is widespread in developed countries across Europe, Oceania, the Americas, Japan and Korea (Lu et al., 2006). The GT4 are classified into 7 subtypes, such as 4a-g and is endemic to China and Southeast Asia but has emerged in

indigenous cases in Europe over the past decade (Boyer et al., 2012).

6. Symptoms of HEV

Some HEV infected people have no symptoms but can still spread the virus to others. Symptoms usually start 3-6 weeks with an average 40 days after the HEV infection; some cases symptoms may occur from 15-64 days after infection (Heymann, 2015). The symptoms of hepatitis E are jaundice, fever, tiredness, loss of appetite, malaise, anorexia, nausea, vomiting, abdominal pain, joint pain, hepatomegaly, pruritus, dark urine, pale stools, and arthralgia (Mirazo et al., 2014). An altered immune status, hormonal levels, and viral factors may be related to the severity of the disease. The HEV can cause acute liver failure that can lead to death. The HEV infection can cause fulminant hepatitis failure, such as cerebral edema, disseminated intravascular coagulation (DIC), and encephalopathy at a higher rate with a mortality rate of up to 30% (Wu et al., 2020).

The HEV patient has a higher risk of fulminant hepatitis and may cause acute liver failure in a few days. It causes acute hepatitis that recovers completely without causing any longstanding chronic hepatitis (Lewis et al., 2010). Acute hepatitis is marked by sudden and massive death of the hepatocytes over a short period of time. It creates a lifelong immunity following natural infection. Clinical symptoms are usually concurrent with increases in liver enzyme levels markedly, such as bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (Hoofnagle et al., 2012).

7. Transmission of HEV

The HEV can be transmitted via the fecal-oral route, zoonotic route, and blood transfusion route. The infection in pregnancy is also associated with vertical transmission with significant perinatal morbidity and mortality (Wu et al., 2020). The HEV is usually spread from animals to humans through the consumption of undercooked and processed pork, deer, camels or shellfish. It can also be spread directly through handling animals. Direct spread of HEV from person to person through blood transfusions is very rare (Grierson et al., 2015).

The HEV can spread from person to person by swallowing foods and drinks that is contaminated with feces from the HEV infected person (Weston et al., 2016). People who live in, or travel to, countries with poor sanitation are at most risk. Most people get hepatitis E from drinking water contaminated with sewage. The transmission of HEV is similar to HAV, and is by the oral-fecal route (enterically), but it may develop into acute liver failure and is associated with higher mortality (Mayr et al., 2018). Other routes of transmission are consumption of contaminated food, such as raw or undercooked meat derived from infected animals and through transfusion of infected blood (Lewis et al., 2010).

Hepatitis E can be spread through the eating food or drinking water in countries with poor sanitation, eating undercooked meat, venison (deer) and wild boar, eating raw shellfish that has been contaminated by sewerage, eating food prepared by an infectious person, direct contact with infectious animals, transmission from a pregnant woman to her baby (Patra et al., 2007). It can be spread through the direct contact with an infected person, such as a household member or sexual partner, or in childcare or healthcare settings (Mirazo et al., 2014).

8. Diagnosis of HEV

Diagnosis can be made indirectly by detecting antibodies against HEV in the serum, or directly by detecting the genome of the virus in blood or other body fluids (Kamar et al., 2014). Diagnosis of hepatitis E depends on clinical and epidemiologic features to detect IgM and IgG anti-HEV in serum. Anti-HEV IgG antibodies are detectable by 3 weeks post immunization and persist for at least 8 weeks (Meng et al., 1997). Serologic tests for IgG against HEV are insufficient to identify HEV infection. Chronic HEV infection is defined as an HEV viremia for more than 3 months with prolonged cholestasis and hematological malignancy. This condition has mainly been reported for HEV-3 and 4, leading to life-threatening liver fibrosis and cirrhosis (Lhomme et al., 2020).

9. Treatment of HEV

The HEV infections are usually self-limiting and asymptomatic in immunocompetent individuals. Prevention is the most effective policy to protect HEV (Wedemeyer et al., 2012). No effective and specific treatments against HEV infection have been developed yet, and also there is no HEV vaccine available, and treatment is palliative and supportive (Mirazo et al., 2014).

Current therapeutics used to treat HEV infection are the nucleoside analog ribavirin and pegylated interferon-α (PEG IFN-α) (Kamar et al., 2014). The broad-range antiviral ribavirin inhibits the replication of various RNA and DNA viruses. It is the only recommended treatment option for patients in whom reversal of immunosuppression is not successful and for other patients suffering from severe acute hepatitis E or liver failure (Kamar et al., 2010). The IFN-α is generally contraindicated after transplantation of most organs and is only recommended in liver transplant patients who do not respond to ribavirin (Kang et al., 2018). A Chinese

vaccine has been demonstrated to be protective against HEV in the general population and seems to be safe in pregnancy; however, its safety and efficacy is not determined (Wu et al., 2020).

10. Conclusions

From this study, we have observed that the HEV infection is a significant cause of acute and chronic viral hepatitis worldwide. It is now recognized as an important global health problem in both developing and industrialized countries for numerous morbidity and mortality. Still, it poses several challenges and is not fully understood. The disease is potentially preventable by simple improving hygiene and sanitary measures, and clean and healthy food intake, avoiding consumption of undercooked meat, improving prognosis and avoiding other existing difficulties. Moreover, it can be treated with medications, therapies, and nutrition supports.

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A Study on the Development and Promotion Strategies of Comprehensive Informatization Solutions in Smart Healthcare

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Abstract

This paper presents the development and promotion process of comprehensive informatization solutions for smart healthcare. With the rapid advancement of smart healthcare, medical informatization has become a crucial means to enhance the quality and efficiency of medical services. This study optimizes the Multi-Channel Integrated Promotion System (MCIPS) and conducts pilot applications in medical institutions of various scales and types. By collecting and analyzing extensive data to assess the effectiveness of the solutions, the results demonstrate that the comprehensive solutions significantly improve the informatization level and service efficiency of medical institutions, optimize medical processes, and enhance the work efficiency of medical staff and patient satisfaction. Moreover, through systematic data analysis and feedback mechanisms, a mature promotion model has been established, providing strong support for nationwide implementation.

Keywords: smart healthcare, informatization, comprehensive solutions, multi-channel promotion, pilot application, effectiveness evaluation, medical institutions, service efficiency, data-driven, promotion strategies, medical informatization systems

1. Introduction

1.1 Research Background

With the rapid development of information technology, smart healthcare has emerged as a significant direction for the global medical industry. By integrating advanced technologies such as the Internet of Things (IoT), big data, and artificial intelligence (AI), smart healthcare optimizes the allocation of medical resources, enhances the efficiency and quality of medical services, and improves patient experiences. In recent years, the Chinese government has issued a series of policies to promote the construction of medical informatization, such as the "Healthy China 2030" Plan, which explicitly calls for the vigorous development of smart healthcare to elevate the level of intelligent medical services. However, the promotion of smart healthcare still faces numerous challenges. Medical institutions of different scales and types exhibit significant differences in informatization foundations, technological needs, and resource investments, necessitating highly customized solutions for the promotion of smart healthcare informatization. Additionally, the particular nature of the medical industry demands that informatization systems possess high levels of security, stability, and reliability, imposing stricter requirements on technological development and promotion.

1.2 Research Objectives

This study aims to explore effective development and promotion models for comprehensive informatization solutions in smart healthcare. It focuses on developing a set of smart healthcare informatization solutions that meet the needs of medical institutions and can be efficiently promoted. By optimizing the Multi-Channel Integrated Promotion System (MCIPS), which integrates online and offline channels, partner resources, and user feedback mechanisms, the promotion efficiency and effectiveness are enhanced. Pilot applications in medical

institutions of various scales and types are conducted to collect and analyze relevant data, assessing the solutions' impact on the informatization level and service efficiency of medical institutions. Successful experiences and challenges are summarized to form a replicable and promotable model, providing references for nationwide implementation.

1.3 Research Significance

This study holds significant theoretical and practical importance. Theoretically, current research on the promotion of smart healthcare informatization mainly focuses on technological development and application, with a lack of systematic studies on promotion models. By constructing and optimizing the promotion model for comprehensive informatization solutions in smart healthcare, this study offers new perspectives and methodologies for theoretical research in this field. Practically, through pilot applications and effectiveness evaluations, this study provides actionable reference solutions for medical informatization construction, facilitating the widespread application of smart healthcare across the country, enhancing the overall level of medical services, improving patient experiences, and promoting high-quality development in the medical industry.

2. Overview of Comprehensive Informatization Solutions for Smart Healthcare

2.1 Definition and Connotation of the Solutions

Comprehensive informatization solutions for smart healthcare represent an innovative medical management model. These solutions utilize modern information technologies to integrate medical resources, optimize service processes, and enhance the scientific and precise nature of medical decision-making, thereby achieving intelligent, efficient, and humanized medical services. Centered around patients, these solutions break down information silos, enable the sharing and collaboration of medical data, and cover multiple aspects such as patient information management, optimization of medical processes, resource integration, and decision support. By leveraging tools like the Multi-Channel Integrated Promotion System (MCIPS), these solutions provide comprehensive informatization support to medical institutions.

2.2 Main Functions and Features of the Solutions

The solutions possess several core functions, including Hospital Operating System (HOS), Electronic Medical Record (EMR), Picture Archiving and Communication System (PACS), Data Platform, and Intelligent Decision Support System (IDSSS). These functions enable comprehensive digital management of medical information, support for imaging diagnosis, data analysis, and decision-making, while also extending the boundaries of medical services through internet-based medical platforms and smart elderly care systems to enhance patient experiences. The solutions are characterized by high integration and flexibility, employing modular design to allow customizable configurations based on different needs and strictly adhering to data security and privacy protection regulations.

2.3 Technical Architecture of the Solutions

The technical architecture is designed in layers, comprising the infrastructure layer, data management layer, application layer, and user interaction layer. The infrastructure layer provides hardware and network support, the data management layer is responsible for data storage, management, and analysis, the application layer contains multiple subsystems to achieve business collaboration, and the user interaction layer offers convenient operational interfaces. The technological selection includes cloud computing, big data, artificial intelligence, and network security technologies to meet the demands of efficiency, intelligence, and security.

3. Development of Comprehensive Informatization Solutions for Smart Healthcare

3.1 Requirements Analysis

Requirements analysis is crucial in the development of comprehensive informatization solutions for smart healthcare. Through surveys conducted in 50 medical institutions nationwide, significant differences were found in data sharing and collaboration, system functional needs, and user experience. In terms of data sharing, 80% of institutions reported that their existing systems failed to achieve cross-departmental or cross-institutional data sharing, leading to severe information silos. For example, Zhongshan Hospital had a patient referral repeat examination rate as high as 30% due to the lack of a data-sharing mechanism. Regarding system functional needs, tertiary hospitals were more concerned with intelligent auxiliary diagnosis systems and imaging analysis, with an expected popularity rate of 70%; primary medical institutions, on the other hand, had higher demands for electronic medical record systems and remote medical functions, with expected popularity rates of 85% and 75%, respectively. In terms of user experience, system response times exceeding 3 seconds significantly reduced the efficiency of medical staff. After reducing the response time from 3 seconds to 1 second at Guangming Hospital, the operational efficiency of medical staff increased by 25%, and patient waiting times decreased by 15% (Yoon, H.-J., 2019). Based on these findings, the core requirements for the comprehensive informatization solutions for

smart healthcare were identified: to achieve efficient data sharing and collaboration, provide customized functions, and optimize system performance.

Table 1.

Category of Demand	Survey Data
Data Sharing and Collaboration	80% of institutions report that their current systems cannot achieve data sharing across departments or institutions, leading to severe information silos.
System Functionality Demand	The expected adoption rate for tertiary hospitals is 70%.
	The demand adoption rates for primary healthcare institutions are 85% and 75%, respectively.
User Experience	Response times exceeding 3 seconds significantly reduce the efficiency of medical staff.

3.2 System Design and Development

Based on the requirements analysis, the system design and development followed principles of modularity, scalability, and security, employing agile development methods to rapidly respond to changing demands through iterative development and continuous integration. The system architecture adopted a layered design, including the infrastructure layer, data management layer, application layer, and user interaction layer. Technologically, the selection included cutting-edge technologies such as cloud computing, big data, and artificial intelligence to meet the demands of efficiency, intelligence, and security. During the development process, particular attention was paid to security and privacy protection, with technical means such as encrypted transmission and access control employed to ensure data security. The system has passed the national information security level three certification.

3.3 System Integration and Testing

System integration and testing are key stages in the development process. During integration, middleware technology was utilized to achieve seamless collaboration and data interaction among subsystems, significantly enhancing system performance. Testing was conducted in multiple stages, including unit testing, integration testing, system testing, and user acceptance testing, to comprehensively verify the system's functionality, performance, security, and compatibility. During testing, the system demonstrated stable response times of less than 2 seconds under high concurrency, supporting over 1,000 concurrent users, with data accuracy reaching 99.9% and transmission success rates exceeding 99%. Through integration and testing, the system's functionality and performance were verified, potential issues were optimized, and the system was successfully launched in multiple pilot medical institutions, laying the foundation for its promotion.

4. Promotion Strategies for Comprehensive Informatization Solutions for Smart Healthcare

4.1 Design and Optimization of the Multi-Channel Integrated Promotion System (MCIPS)

The Multi-Channel Integrated Promotion System (MCIPS) is the core tool for promoting comprehensive informatization solutions for smart healthcare, and its design and optimization directly affect the promotion effectiveness. MCIPS integrates various online and offline promotion channels, including social media, industry exhibitions, partner promotion, online seminars, and offline training. By analyzing the promotion effectiveness data of different channels, it was found that social media and industry exhibitions had the most significant promotion effects, bringing in 35% and 30% of potential customer traffic, respectively. Partner promotion contributed 20% of the traffic. Although online seminars and offline training had relatively lower traffic, they had higher conversion rates of 15% and 10%, respectively.

To further optimize MCIPS, in-depth analysis and adjustment of each channel were carried out. In terms of social media, by precisely targeting the target audience and optimizing content strategies, the potential customer traffic increased by 20%. At industry exhibitions, by showcasing actual application cases and live demonstrations, more attention from medical institutions was attracted, and the potential customer traffic from exhibitions increased by 25%. Meanwhile, cooperation with industry partners was strengthened through joint promotion and resource sharing, resulting in an 18% increase in traffic from partner channels. Additionally, the content and format of online seminars and offline training were optimized to make them more targeted and attractive, increasing their conversion rates by 10% and 8%, respectively.

Table 2.

Promotion Channels	Initial Effect	Optimized Effect
Social Media	Potential customer traffic accounts for 35%	Potential customer traffic increases by 20%
Industry Trade Shows	Potential customer traffic accounts for 30%	Potential customer traffic increases by 25%
Partner Promotion	Potential customer traffic accounts for 20%	Traffic increases by 18%
Online Seminars	Low traffic, conversion rate of 15%	Conversion rate increases by 10%
Offline Training	Low traffic, conversion rate of 10%	Conversion rate increases by 8%

4.2 Construction of the Promotion Model

Constructing an effective promotion model is key to ensuring the widespread application of comprehensive informatization solutions for smart healthcare. Based on the scale, type, and informatization foundation of medical institutions, differentiated promotion models were designed. For tertiary hospitals, the focus was on demonstrating the advanced functions of the solutions, such as intelligent auxiliary diagnosis systems and medical imaging analysis. Through customized demonstrations and case sharing, 70% of tertiary hospitals participated in pilot applications. For secondary hospitals, the emphasis was on the solutions' advantages in enhancing the efficiency and quality of medical services. Through online seminars and offline training, 60% of secondary hospitals participated. For primary medical institutions, the promotion focused on electronic medical record systems (EMR) and remote medical functions. Through partner promotion and industry exhibitions, 85% of primary medical institutions participated.

During the promotion process, a comprehensive customer feedback mechanism was established. Regular follow-ups and online surveys were conducted to collect the usage experiences and suggestions of medical institutions. During the pilot application stage, feedback data from 100 medical institutions were collected, with 90% indicating that the solutions significantly improved the efficiency of medical services and 80% reporting increased patient satisfaction. Based on this feedback, the solutions were optimized and improved to further enhance the promotion effectiveness.

4.3 Problems and Countermeasures in the Promotion Process

Firstly, some medical institutions had a low acceptance of new technologies, worrying about the complexity and operational difficulty of the systems. To address this issue, training and technical support were strengthened. Through online training courses and offline training activities, medical staff were helped to quickly master the use of the systems. Detailed operation manuals and online help documents were also provided to ensure that medical staff could obtain support at any time during use. As a result, the complaint rate regarding system operational difficulty decreased by 65%. (Yoon, H.-J., 2019)

Secondly, some medical institutions were concerned about the security and data privacy of the systems. To dispel these concerns, the system's security certifications and data protection measures, such as encrypted transmission, access control, and data backup, were showcased. Security training and consulting services were also provided to help medical institutions better understand and apply these security measures. Through these efforts, concerns regarding data security were reduced by 73%.

Lastly, budget constraints were encountered during the promotion process. To address this issue, flexible pricing strategies and installment payment plans were introduced to lower the initial investment threshold for medical institutions. Meanwhile, the long-term benefits and cost-saving potential of the solutions were demonstrated to help medical institutions understand the value of the investment. As a result, the promotion resistance caused by budget issues decreased by 52%.

Table 3.

Category of Issue	Effectiveness Evaluation
Operational Complexity	Complaints about system operational complexity have decreased by 65%.
Security and Data Privacy	Concerns regarding data security have been reduced by 73%.
Limited Budget	Resistance to promotion due to budget constraints has decreased by 52%.

5. Pilot Application and Effectiveness Evaluation of Comprehensive Informatization Solutions for Smart Healthcare

5.1 Implementation of Pilot Applications

To comprehensively evaluate the actual effectiveness of comprehensive informatization solutions for smart healthcare, pilot applications were conducted in representative medical institutions across the country. The pilot medical institutions included Beijing Union Medical College Hospital (tertiary hospital), Shanghai Pudong New District People's Hospital (secondary hospital), and Guangzhou Baiyun District Community Health Service Center (primary medical institution). These institutions, with significant differences in scale, function, and informatization level, provided a rich context for the comprehensive evaluation of the solutions.

At Beijing Union Medical College Hospital, the focus was on promoting the intelligent auxiliary diagnosis system and the Picture Archiving and Communication System (PACS). Through close cooperation with the hospital's information department, the system was deployed and initially trained within just two months. After the system went live, the diagnostic efficiency of the hospital's radiology department significantly improved. The average diagnostic time was reduced from 30 minutes to 20 minutes, and the diagnostic accuracy increased from 85% to 95%. Moreover, the intelligent auxiliary diagnosis system helped doctors identify more potential issues in complex cases, thereby enhancing the quality of medical care.

At Shanghai Pudong New District People's Hospital, the Electronic Medical Record (EMR) system and the Hospital Operating System (HOS) were implemented. During the pilot process, it was found that the implementation of the system had a positive impact on the hospital's daily operations. The time taken by medical staff to enter medical records was reduced by 25%, and the completeness and accuracy of medical records increased by 30% (Chen, H.S., Jarrell, J.T., Carpenter, K.A., Cohen, D.S. & Huang, X., 2019). Through the data analysis function of the HOS system, the hospital's management could gain a clearer understanding of the hospital's operational status, optimize resource allocation, and improve overall operational efficiency.

At Guangzhou Baiyun District Community Health Service Center, the remote medical system and the smart elderly care management information system were promoted. Through the remote medical system, community residents could conveniently consult with experts from higher-level hospitals via video consultations, reducing the need for patients to travel to larger hospitals. During the pilot period, the remote medical system was used more than 50 times per week, and patient satisfaction increased from 66% to 85%. The smart elderly care management information system provided convenient health monitoring and management services for community-based elderly care institutions, enhancing the quality and efficiency of elderly care services.

Table 4.

Category of Issue	**Effectiveness Evaluation**
Operational Complexity	Complaints about system operational complexity have decreased by 65%.
Security and Data Privacy	Concerns regarding data security have been reduced by 73%.
Limited Budget	Resistance to promotion due to budget constraints has decreased by 52%.

5.2 Data Collection and Analysis

During the pilot application process, a large amount of data was collected through various means to comprehensively evaluate the effectiveness of the solutions. Data collection was primarily conducted through system logs, user feedback, questionnaires, and on-site interviews. System logs recorded key indicators such as system usage frequency, operation response time, and data transmission success rate. User feedback was collected through online surveys and regular follow-ups, covering the usage experiences and suggestions of medical staff and patients. Questionnaires and on-site interviews provided deeper insights into the impact of the system on the operation of medical institutions and patient experiences.

Through analysis of the collected data, it was found that the comprehensive informatization solutions for smart healthcare achieved significant results in multiple aspects. For example, at Beijing Union Medical College Hospital, after the system went live, the data transmission success rate for medical imaging reached 99.5%, and the accuracy and efficiency of imaging diagnosis were significantly improved. At Shanghai Pudong New District People's Hospital, the completeness and accuracy of medical records increased by 28%, and the work efficiency of medical staff improved by 20% (Clohessy, T., Hasselgren, A., El-Gazzar, R. & Stendal, K., 2020). At Guangzhou Baiyun District Community Health Service Center, both the usage frequency and patient satisfaction of the remote medical system increased significantly, and the smart elderly care management information system provided more efficient service support for community-based elderly care institutions.

Additionally, the data analysis revealed some potential issues. For instance, in some medical institutions, the complexity of system operations led to higher training needs for medical staff. In response to this issue, the system interface was further optimized, the operation process was simplified, and more online help functions were added. As a result, the complaint rate regarding system operational difficulty decreased by 42%.

5.3 Effectiveness Evaluation

At Beijing Union Medical College Hospital, the implementation of the intelligent auxiliary diagnosis system and the Picture Archiving and Communication System (PACS) significantly improved diagnostic efficiency and accuracy. The diagnostic time was shortened by 33%, and the diagnostic accuracy increased by 10 percentage points. Moreover, the data analysis function of the system helped the hospital's management better optimize resource allocation, thereby improving the overall operational efficiency of the hospital.

At Shanghai Pudong New District People's Hospital, the implementation of the Electronic Medical Record (EMR) system and the Hospital Operating System (HOS) significantly improved the informatization level of the hospital. The time taken by medical staff to enter medical records was reduced by 25%, and the completeness and accuracy of medical records increased by 30%. Through the data analysis function of the HOS system, the hospital's management could gain a clearer understanding of the hospital's operational status, optimize resource allocation, and improve overall operational efficiency.

At Guangzhou Baiyun District Community Health Service Center, the implementation of the remote medical system and the smart elderly care management information system significantly improved the quality of community medical services and elderly care services. The usage frequency of the remote medical system reached more than 50 times per week, and patient satisfaction increased from 70% to 85%. The smart elderly care management information system provided convenient health monitoring and management services for community-based elderly care institutions, enhancing the quality and efficiency of elderly care services.

6. Conclusions

6.1 Research Summary

This study focused on the development and promotion of comprehensive informatization solutions for smart healthcare. Through requirements analysis, system design, pilot application, and effectiveness evaluation, the significant effectiveness of the solutions in enhancing the efficiency and quality of medical services was verified. The core needs of medical institutions for data sharing, customized system functions, and user experience optimization were identified, and a layered architecture solution based on cloud computing, big data, and artificial intelligence technologies was developed accordingly. The construction and optimization of the Multi-Channel Integrated Promotion System (MCIPS) further enhanced the promotion effectiveness of the solutions. The successful implementation of pilot applications at Beijing Union Medical College Hospital, Shanghai Pudong New District People's Hospital, and Guangzhou Baiyun District Community Health Service Center significantly shortened diagnostic time (by 33%), increased the completeness and accuracy of medical records (by 30%), and raised patient satisfaction from 70% to 85%.

6.2 Research Limitations and Future Outlook

Despite the positive outcomes achieved, there are still some limitations in this study. The intelligent auxiliary diagnosis system needs further improvement in accuracy and efficiency when dealing with complex cases. The acceptance of new technologies by some medical institutions is still low, resulting in significant promotion resistance. Although data security and privacy protection have passed certifications, continuous optimization is necessary. Future research can further deepen the functions of the intelligent auxiliary diagnosis system and develop more targeted promotion strategies to reduce promotion resistance and increase the popularity of the solutions. With the development of technologies such as 5G and the Internet of Things, smart healthcare will evolve towards more intelligent and personalized directions, and data security and privacy protection will become key research focuses. This study provides practical guidance for the promotion of comprehensive informatization solutions in smart healthcare and lays the foundation for the widespread application of smart healthcare.

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Protective and Curative Effects of Virgin Coconut Oil on Acetaminophen-Induced Hepatotoxicity in Adult Wistar Rat

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Abstract

Acetaminophen-induced hepatotoxicity is a well-documented consequence of acetaminophen overdose, necessitating the exploration of therapeutic interventions to develop safer alternatives to synthetic drugs. In this study, we investigated the potential effects of Virgin Coconut Oil (VCO) on acetaminophen (PCM)-induced hepatotoxicity. Thirty-six Wistar rats were divided into twelve groups as follows: Groups 1 and 2 received Normal Saline for 20 and 40 days, respectively; Groups 3 and 4 were administered 750mg/kg of PCM for 20 and 40 days, respectively. Group 5 received 2.5ml/kg of VCO for the initial 10 days followed by 750mg/kg of PCM for the subsequent 10 days. Group 6 received VCO at 2.5ml/kg for the first 20 days followed by 750mg/kg of PCM for the remaining 20 days. Groups 7 and 8 received VCO at 5ml/kg for the initial 10 and 20 days, respectively, followed by PCM administration for the subsequent 10 and 20 days. Groups 9 and 10 were administered 750mg/kg of PCM for the initial 10 and 20 days, respectively, followed by VCO at 2.5ml/kg for the remaining 10 and 20 days. Lastly, Groups 11 and 12 received 750mg/kg of PCM for the initial 10 and 20 days, respectively, followed by VCO at 5ml/kg for the remaining 10 and 20 days. Acetaminophen administration resulted in a significant ($p \leq 0.05$) decrease in the final body weight of PCM-treated groups, while a significant ($p \leq 0.05$) increase in body weight was observed in the negative control, pre-treated, and post-treated groups with VCO. Notably, PCM-treated groups exhibited a significant ($p \leq 0.05$) increase in liver weight compared to negative control and VCO-treated groups. Liver enzyme levels including ALP, ALT, AST, and GGT remained within normal reference ranges in negative control and VCO-treated groups, whereas a significant ($p \leq 0.05$) increase was observed in the positive control groups. Additionally, levels of GPx, SOD, and CAT were significantly ($p \leq 0.05$) decreased in the positive control group compared to the negative control and VCO-treated groups. Overall, the findings of this study demonstrate the potential ameliorating effect of VCO against PCM-induced liver toxicity, highlighting its potential therapeutic utility in mitigating hepatotoxicity.

Keywords: hepatotoxicity, Paracetamol, curative, protective, N-Acetylcysteine, Virgin Coconut Oil

1. Introduction

Liver is the largest organ in the human body and key organ of metabolism, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, and detoxification (Opoku *et al*., 2007). It is continuously and variedly exposed to xenobiotic, environmental pollutants, and chemotherapeutic agents because of its strategic placement in the body (Ibrahim *et al.*, 2008).

Acetaminophen also known as N-acetyl-para-aminophenol (Paracetamol) was discovered in 1889. It is an active metabolite of phenacetin, a compound that was used for its good analgesic and antipyretic properties until it was implicated in analgesic-abuse (Larsen & Wendo, 2014). When acetaminophen is consumed above its therapeutics dosage will lead to hepatotoxicity which is its commonest and most remarkable feature (Larsen & Wendo, 2014). When acetaminophen is taken orally, its absorption occurs rapidly in the duodenum, owing to its

property as a weak acid (McGill & Jaeschke, 2013). It will rapidly metabolize in the liver and majority is eliminated by conjugation to nontoxic sulfated and glucuronidated metabolites and a small percentage of it will undergo oxidation with the help of cytochrome p-450 enzyme resulting in the formation of highly reactive N-acetyl-p-benzoquinone-imine (NAPQI) (Bunchorntavakul & Reddy, 2013; McGill & Jaeschke, 2013). In the normal process of detoxification, this reactive NAPQI is detoxified by the antioxidant enzyme glutathione (GSH) and always maintains equilibrium to neutralize the toxic environment (Song *et al*., 2014). However, when acetaminophen is consumed above its therapeutical dosage, it leads to excessive production of NAPQI that can inflict a shift in this equilibrium due to the saturation of sulfation and glucuronidation process and depletion of GSH, which creates an oxidative stress condition (Dai *et al*., 2006). As a result, progressively more reactive oxygen species (ROS) will be released and that will trigger the cellular necrosis by organelle swelling along with membrane dysfunction through disruption of the mitochondrial membrane permeability transition pores (Yuan & Kaplowitz, 2013).

Coconut tree (*Cocos nucifera L.*) is considered as a premium gift from nature to mankind (Afka *et al.*, 2021). It is also known as the 'tree of life' since each part of the tree has its own medicinal value (Intahphuak *et al.*, 2010; Gans & Kauwell, 2017). Virgin Coconut Oil is recognized as a functional food and the public awareness of it is increasing day by day. Virgin coconut oil is a naturally processed, chemically free and additive free product from fresh coconut meat or its derivatives (coconut milk and coconut milk residue), which has not undergone any chemical processing after extraction (Rajagopal & Rajeev, 2017). It has a mild to intense fresh coconut scent depending on the type of process used for production. Virgin Coconut oil is extracted from fresh coconut milk obtained from matured coconut of 12 months old. It can be consumed in its natural state without the need for further processing (Rajagopal & Rajeev, 2017). It is processed using a low heat process and its nutritional value and health benefits have been recognized for many years. So, it has a significant role in our diet (Kamariah *et al.*, 2008; Widianingrum & Salasia, 2021).

2. Materials and Methods

Chemicals: Acetaminophen (Emzor Pharmaceutical Industries Limited, Nigeria) was procured from Vincal Pharmacy Limited, Wadata, Makurdi. The drug is in solid form and was dissolved in distilled water and dosage was calculated based on body weight in grams (g) and administered orally via gavage syringe.

Induction of Hepatotoxicity: Toxicity was induced by daily doses of 750 mg/kg body weight of PCM orally via gavage following reported toxicity ranges, exposure routes and concentrations (Uchendu *et al*., 2018).

Virgin coconut oil was prepared from the solid endosperm of mature coconut. It was crushed and made into viscous slurry. The slurry was then squeezed through cheese cloth to obtain coconut milk, and it was refrigerated for 48 hours. After 48 hours, the milk was subjected to mild heating (50°C) in a thermostat oven. The obtained virgin coconut oil was filtered through cheese cloth (Nevin & Rajamohan, 2006). The mature copra of Coconut fruit weighed 1 killogram produced 500mls of virgin coconut oil and was stored at room temperature in a propylene ethylene bottle.

2.1 Ethical Considerations

All experimental protocols were in compliance with the laid down ethical guidelines for the use of animals in research, given by the National Committee for Research Ethics in Science and Technology CREC/002.

2.2 Animal Grouping and Administration

The adults Wistar rats (total n=36) were divided into twelve groups and each group contained three (n=3) rats.

Group 1 and 2 (Normal Saline for 20 and 40 days respectively), 3 and 4 (750mg/kg of PCM for 20 and 40 days respectively). Group 5: 2.5ml/kg of VCO for first 10 days, 750mg/kg of PCM for last 10 days. Group 6: VCO at 2.5mls/kg for first 20 days, 750mg/kg of PCM for last 20 days. Group 7 and 8: VCO at 5ml/kg for the first 10 days and 20 days then 750mg/kg of PCM for the last 10 and 20 days. Group 9 and 10: 750mg/kg of PCM for the first 10 and 20 days then VCO at 2.5mls/kg for the last 10 and 20 days. Group 11 and 12: 750mg/kg of PCM for the first 10 and 20 days then VCO at 5ml/kg for the last 10 and 20 days respectively.

Animal Sacrifice and Sample Collection: At the end of the experimental period, all the animals were fasted overnight and weighed at the point of sacrifice using the LS series electronic weighing balance manufactured (ORMA, Italy). They were anesthetized with mild chloroform anesthesia and sacrificed via cervical dislocation. Blood was collected via cardiac puncture with the aid of a needle mounted on a 5 mL syringe (Hindustan Syringes and Medical Devices Ltd., Faridabad, India). The samples were collected into tubes containing 2% sodium oxalate, centrifuged at 3000 rpm for 15 min using a tabletop centrifuge and the serum extracted. The sera were separated and stored in aliquots at -25°C for biochemical assays of specific liver enzymes. The liver was harvested after the abdominal incision, washed three times in normal saline and blotted on ash-free filter paper for macroscopic inspection. It was then fixed in a 10% formal saline for routine histological processing.

2.3 Biochemical Assays of Specific Liver Enzymes

2.3.1 Alanine Aminotransaminase (ALT) Activity

Reitman-Frankel colorimetric method using a Quimica Clinica Applicada (QCA) test kit. ALT activity was measured by monitoring the concentration of pyruvate hydrazone formed with 2, 4-dinitrophenylhydrazine which is proportional to its concentration at 505nm.

2.3.2 Aspartate Aminotransferase Activity (AST)

This parameter was done using the Reitman-Frankel colorimetric method (Reitman & Frankel, 1957) for *invitro* determination of GOT/AST in serum using a Quimica Clinica Applicada (QCA) test kit. I measured AST activity by monitoring the concentration of oxaloacetate hydrazone formed with 2, 4 — dinitrophenylhydrazine spectrophotometrically at 505nm.

2.3.3 Alkaline Phosphatase (ALP) Activity

Phenolphthalein monophosphate method for the in vitro determination of alkaline phosphatase in serum using Quimica Clinica Applicada (QCA) test kit. Alkaline phosphatase acts upon the AMP-buffered sodium thymolphthalein monophosphate. The addition of the alkaline reagent stops the enzyme activity and simultaneously develops a blue chromogen which can be measured photometrically at wavelength of 550nm.

2.4 Estimation of Oxidative Stress Makers

Gamma-Glutamyl Transferase (GGT): The serum was separated by centrifugation (3600 rpm for 15 min) for the determination of serum. Gamma glutamyl transferase (GGT) levels using Quimica Clinica Applicada (QCA) commercial test kits indication.

Estimation of lipid peroxidation (Malondialdehyde (MDA): Lipid peroxidation in the tissue was estimated colorimetrically by thiobarbituric acid reactive substances (TBARS) method of Buege and Aust (1978). A principal component of TBARS is malondialdehyde (MDA), a product of lipid peroxidation. In brief, 0.1 ml of tissue in Tris-HCl buffer, pH 7.5 was treated with 2 ml of (1:1:1 ratio) TBA-TCA-HCl reagent (thiobarbituric acid 0.37%, 0.25 N HCl and 15% TCA) and placed in water bath for 15 min, cooled. The absorbance of clear supernatant was measured against reference blank at 535 nm. Concentration was calculated using the molar absorptivity of malondialdehyde which is 1.56×10^5 M^{-1} cm^{-1} and expressed as nmol/mg protein.

Measurement of Glutathione peroxidase (GPx) activity: The amount of GPx was determined using a commercially available kit (Ransel kit, Randox Laboratories Ltd, Crumlin, UK) by measuring the rate of oxidation of NADPH at 340 nm. A unit of enzyme was expressed as the amount of enzyme needed to oxidize 1nmol of NADPH oxidase/minute.

Assay of Superoxide Dismutase (SOD) activity: Superoxide dismutase activity was measured according to the method of Winterbourn *et al.* (1975) as described by Rukmini *et al*. (2004). The principle of the assay was based on the ability of SOD to inhibit the reduction of nitro-blue tetrazolium (NBT). Briefly, the reaction mixture contained 2.7 ml of 0.067M phosphate buffer, pH 7.8, 0.05 ml of 0.12mM riboflavin, 0.1 ml of 1.5mMNBT, 0.05 ml of 0.01M methionine and 0.1 ml of enzyme samples. Uniform illumination of the tubes was ensured by placing it in air aluminum foil in a box with a 15W fluorescent lamp for 10 minutes. Control without the enzyme source was included. The absorbance was measured at 560nm. One unit of SOD was defined as the amount of enzyme required to inhibit the reduction of NBT by 50% under specific conditions. Activity of enzyme was expressed as units /mg protein.

Assay of catalase (CAT) activity: Catalase activity was measured according to the method of Aebi (1983). Tissue (0.1 ml) was pipetted into cuvette containing 1.9 ml of 50mM phosphate buffer, pH 7.0. Reaction was started by the addition of 1.0 ml of freshly prepared 30% (v/v) hydrogen peroxide (H_2O_2). The rate of decomposition of H_2O_2 was measured spectrophotometrically from changes in absorbance at 240 nm. Activity of enzyme was expressed as units /mg protein.

Statistical Analysis: All data will be expressed as mean ± SEM. The level of homogeneity among the groups will be tested using Analysis of Variance (ANOVA) as described by Snedecor and Cochran (1980**)**. Where heterogeneity occurred, the groups will be separated using Duncan Multiple Range Test (DMRT). A value of $p < 0.05$ will be considered to indicate a significant difference between groups as described by Mathur *et al.*, (2008). Analysis of data will be done using both electronic calculator and Statistical Package for Social Sciences (SPSS version 20.0).

3. Results

3.1 Gross Anatomical Parameters

Table 1, there was significant ($p \leq 0.05$) increase in body weight of the acute negative control compared to the positive control. There was significant ($p \leq 0.05$) decrease in the body weight of the positive control groups

compared to the groups pre-treated or post-treated with VCO. There was a significant ($p \leq 0.05$) increase in initial body weight, final weight and body weight differences between the control groups (1&2) and the groups post-treated and pre-treated with acetaminophen and VCO or Acetaminophen.

Table 1. Effect of Virgin Coconut Oil and Paracetamol on the gross anatomical parameters of Wistar rat

Grp	Treatment	Initial Body Wt. (g)	$^{+}$Final Body Wt. (g)	$^{+}$Body Wt. Differences
1	Acute Normal Control (5ml/kg N.S)	200.2±7.4	205.4±1.4	5.2±7.7
2	Chronic Normal Control (5ml/kg N.S)	208.5±3.5	220.5±14.8	12.0±11.3
3	Acute Positive control (750mg/kg PCM)	207.8±4.0	190.8±12.4	-17.0±16.4
4	Chronic Positive control (750mg/kg PCM)	210.0±0.1	205.5±30.9	-5.4±30.9
5	Acute Protective (2.5ml/kg VCO+PCM)	182.5±1.3	188.1±4.5	5.5±3.1
6	Chronic Protective (2.5ml/kg VCO+PCM)	186.8±6.5	208.8±4.5	21.9±2.0
7	Acute Protective (5ml/kg VCO+PCM)	161.8±5.9	176.2±10.8	14.4±4.9
8	Chronic Protective (5ml/kg VCO+PCM)	141.8±0.9	167.3±23.9	25.5±22.9
9	Acute Curative (PCM+2.5ml/kg VCO)	178.3±11.3	184.1±10.9	12.9±0.3
10	Chronic Curative (PCM+2.5ml/kg VCO)	198.8±11.4	200.9±40.9	22.6±29.4
11	Acute Curative (PCM+5ml/kg VCO)	198.8±3.1	202.5±15.3	3.7±12.2
12	Chronic Curative (PCM+5ml/kg VCO)	187.6±3.1	237.4±15.48	39.8±18.5

$^{+}$represents significant a non-significant ($p > 0.05$) effect as shown in ANOVA.

3.2 Liver Function Enzymes

Table 2 showed no significant ($p > 0.05$) difference in the activity level of AST and ALT in groups treated with normal/ Saline (group 1 and 2). There was significant increase ($p \leq 0.05$) in the activity of AST and ALT in group (3 and 4) that were treated with PCM alone when compared to those of the (group 5 to 12) which were pre-treated with VCO and post treated with VCO. There was no significant increase ($p > 0.05$) in the activity of AST and ALT among the groups that had a post-treatment or pre-treatment of VCO (groups 5-12).

Table 2. Effect of Virgin Coconut Oil and Acetaminophen on liver function test (Aspartate aminotransferase and Alanine transaminase) of adults Wistar rat

Groups	Treatment	AST(U/L)	ALT (U/L)
1	Acute Normal Control (5ml/kg N.S)	73.1±4.8	37.0±4.3
2	Chronic Normal Control (5ml/kg N.S)	70.3±2.7	55.7±1.9
3	Acute Positive control (750mg/kg PCM)	109.5±4.8	77.0±8.5*
4	Chronic Positive control (750mg/kg PCM)	108.0±2.5*	90.0±4.3*
5	Acute Protective (2.5ml/kg VCO+PCM)	81.5±0.7**	64.6±5.1**
6	Chronic Protective (2.5ml/kg VCO+PCM)	99.1±14.0**	53.6±0.5**
7	Acute Protective (5ml/kg VCO+PCM)	85.2±8.8**	57.5±10.5**
8	Chronic Protective (5ml/kg VCO+PCM)	81.0±1.4**	53.6±0.7**
9	Acute Curative (PCM+2.5ml/kg VCO)	84.0±0.0**	46.6±16.1**
10	Chronic Curative (PCM+2.5ml/kg VCO)	86.7±0.7**	58.1±0.1**
11	Acute Curative (PCM+5ml/kg VCO)	89.5±2.0**	52.0±1.4**
12	Chronic Curative (PCM+5ml/kg VCO)	90.0±1.3**	69.5±10.6**

*, **represents significant decreases or increase at $p \leq 0.05$ when compared to groups 1 and 2 (negative controls), groups 3 and 4 (positive controls), a groups 5 and 6 (Low-dose Protective) and b groups 9 and 10 (Low-dose curative), group 5-8 (protective groups) and acute d groups (sister groups) respectively.

Table 3 shows no significant increase (p>0.05) in the activity of ALP and GGT in groups (1 and 2) that were treated with only normal Saline. There was significant increase ((p≤0.05) the activity of ALP and GGT in groups (3 and 4) that were treated with only PCM in acute and chronic phase. There was no significant increase in the ALP and GGT in the groups (5 to 12) that were either pre-treated or post treated with VCO or PCM.

Table 3. Effect of Virgin Coconut Oil and Acetaminophen on liver function test (*Alkaline phosphatase and* Gamma-glutamyl transferase) of Wistar rat

Groups	Treatment	ALP(U/L)	GGT (U/L)
1	Acute Normal Control (5ml/kg N.S)	63.5±0.7	11.5±0.6
2	Chronic Normal Control (5ml/kg N.S)	61.6±14.9	11.0±1.3
3	Acute Positive control (750mg/kg PCM)	100.6±3.4*	35.5±3.4*
4	Chronic Positive control (750mg/kg PCM)	95.6±10.5*	32.5±6.3*
5	Acute Protective (2.5ml/kg VCO+PCM)	79.3±3.1**	15.5±0.6**
6	Chronic Protective (2.5ml/kg VCO+PCM)	72.1±1.2**	20.8±3.4**
7	Acute Protective (5ml/kg VCO+PCM)	71.6±0.5**	19.0±5.6**
8	Chronic Protective (5ml/kg VCO+PCM)	73.2±14.1**	15.7±0.5^{**,d}
9	Acute Curative (PCM+2.5ml/kg VCO)	73.2±11.2**	17.5±0.7**
10	Chronic Curative (PCM+2.5ml/kg VCO)	81.5±4.8^{**,d}	19.1±1.2**
11	Acute Curative (PCM+5ml/kg VCO)	77.6±5.0**	25.3±4.1**
12	Chronic Curative (PCM+5ml/kg VCO)	82.2±1.4^{**,d}	13.8±4.9^{**,d}

*, **represents significant decreases or increase at p≤0.05 when compared to groups 1 and 2 (negative controls), groups 3 and 4 (positive controls), groups 5 and 6 (Low-dose Protective) and groups 9 and 10 (Low-dose curative), group 5-8 (protective groups) and Acute groups (sister groups) respectively.

Oxidative Stress Marker: Table 4 There was no significant (p>0.05) increase in the activity level of MDA in the group negative control groups (1 and 2). There was significant (p≤0.05) increase in the activities of MDA in groups (3 and 4) treated with only with PCM while there is no significant (p>0.05) increase the activity of MDA in groups (5 to 12) compared to positive control group (3 and 4) in acute and chronic phases. The Catalase activity in negative control groups (1&2) shows no significant (p>0.05) increase while there is significant (p≤0.05) increase in CAT activity in group (3 and 4) which were treated with PCM only compared to the curative and protected groups (5 to 12).

Table 4. Effect of Virgin Coconut Oil and Acetaminophen on oxidative stress markers Catalase (CAT) and Malondialdehyde (MDA) of Wistar rat

Groups	Treatment	MDA (nmol/mg)	CAT (U/mg protein)
1	Acute Normal Control (5ml/kg N.S)	0.8±0.0	26.5±0.6
2	Chronic Normal Control (5ml/kg N.S)	0.7±0.2	28.0±1.4
3	Acute Positive control (750mg/kg PCM)	1.2±0.1*	15.2±0.1*
4	Chronic Positive control (750mg/kg PCM)	2.2±0.5*	15.1±1.2*
5	Acute Protective (2.5ml/kg VCO+PCM)	0.8±0.1**	24.5±4.9**
6	Chronic Protective (2.5ml/kg VCO+PCM)	0.9±0.1**	19.1±1.6^{**,d}
7	Acute Protective (5ml/kg VCO+PCM)	0.5±0.2**	25.7±4.6**
8	Chronic Protective (5ml/kg VCO+PCM)	0.8±0.0**	21.5±4.8^{**,d}
9	Acute Curative (PCM+2.5ml/kg VCO)	0.7±0.2**	22.5±4.9**
10	Chronic Curative (PCM+2.5ml/kg VCO)	0.8±0.3**	20.1±1.2**
11	Acute Curative (PCM+5ml/kg VCO)	1.2±0.0^{b}	25.0±5.7**
12	Chronic Curative (PCM+5ml/kg VCO)	0.6±0.2^{**,d}	22.5±3.4**

*, **, and d represents significant decreases or increase at ($p \leq 0.05$) when compared to groups 1 and 2 (negative controls), groups 3 and 4 (positive controls), groups 5 and 6 (Low-dose Protective) and groups 9 and 10 (Low-dose curative), group 5-8 (protective groups) and acute groups (sister groups) respectively.

4. Discussion

The result shows a significant ($p \leq 0.05$) increase in body weight of rats in group 1 and 2 as well as the pre-treated and post-treated groups with VCO or PCM at high and low dosages in acute and chronic phase whereas in the positive control groups (3 & 4) shows a significant decrease in the body weight.

The Liver functions enzymes showed a significant ($p \leq 0.05$) increase in the liver enzymes activity level of AST, ALT, ALP and GGT in groups treated with acetaminophen alone when compared to the negative control. This study also demonstrates a fairly normal level of liver function enzymes in the acute groups pre-treated and post-treated with VCO as well of those groups of the chronic phase pre-treated and post-treated with VCO. This aspect is in line with studies by Oyagbemi and Odetola (2010) and Asadollahi *et al*, (2014). These results indicated that the VCO may induce immunomodulation. The treatment could modulate lymphocyte proliferation (Yuniwarti *et al.*, 2012). The aforementioned biomarkers for liver damage are all increased in administration of other inducers of liver injury like CCL4, which share common mechanism of cellular injury with acetaminophen (Anusha *et al*., 2011; Nasir *et al.,* 2013). The increase in serum level of liver function enzymes is due to the damage of hepatocytes by the Acetaminophen metabolite (NAPQI) which cause rupture of the cell membrane resulting in leakage of the enzymes from hepatocytes to the serum, where the level of these enzymes is normally lower, and their serum levels become abnormally increased and the fairly normal level of the liver enzymes in the pre-treated and post-treated groups shows the effective antioxidant activity of VCO (Du *et al*., 2016; Yan *et al*., 2018).

The oxidative stress shows a significant ($p \leq 0.05$) increase in the activity level of MDA and CAT in rats treated with PCM alone when compared to the values gotten from rats of negative control. There was no significant ($p > 0.05$) increase in the activity of MDA and CAT in the groups of pre-treated and post-treated with VCO. This is in line with a study done by Zachariah (2012). The study also shows a significant decrease ($p \leq 0.05$) in the activity of GPx in the groups treated with only PCM (group 3 and group 4), and this is also in line with a study carried out by Uchendu *et al*. (2012). In addition to liberation of liver enzymes, as acetaminophen also induces oxidative stress followed by necrosis and cellular damage (Kaplowitz *et al*., 2015).

CONCLUSION: Based on our present findings, VCOs, regardless of the low dosage (2.5ml) and high dose of 5ml possess a promising hepatoprotective effect and this hepatoprotective effect of VCO may be attributed, partly to its antioxidant activity.

Virgin Coconut oil has been shown to exhibit potent antioxidant activities by ameliorating the effects of acetaminophen-induced hepatotoxicity in acute and chronic phases. This study has proven the protective and curative effect of virgin coconut oil on acetaminophen-induced hepatotoxicity in adult Wistar rats at low and high dosages. Hence, the feasibility of exploring a potential agent for the improved treatment of acetaminophen-induced hepatotoxicity in acute and chronic phases with minimal adverse effects at low cost.

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Microscopic Effect of Tobacco on Human Health: How Tobacco Impacts Gene Expression Levels

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Abstract

Tobacco exposure is commonly linked to airway epithelium and lung diseases, yet its impact on the enzymes that catalyze adenosine-to-inosine (A-to-I) RNA editing remains unclear. The goal of this research is to compare the three gene expression levels, ADAR, ADARB1, ADARB2, between smokers and non-smoker, which play an important role in RNA editing and cellular regulation. RNA-sequence count data for smokers (362 samples) and non-smokers (635) were obtained from the GEO publication "Cigarette Smoking-Associated Isoform Switching and 3' UTR Lengthening Via Alternative Polyadenylation" (GSE171730). Data obtained was first applied with $\log_2$-transformation to dampen outliers, then compared with T-test. The result of the study shows that smoking had no significant effect on ADAR1, but produced robust up-regulation of ADARB1 and ADARB2. These results indicate that tobacco selectively enhances expression of two ADAR paralogs while sparing the ubiquitously expressed ADAR1, pointing to a targeted modulation of the RNA-editing machinery in smokers. Such selective induction may shift global A-to-I editing profiles and contribute to smoking-associated disease risk.

Keywords: smoking, RNA editing, ADAR enzymes, airway epithelium, gene expression, transcriptomics

1. Introduction

For decades, smoking has been associated with increased risk of developing various diseases, including lung and cardiovascular diseases. It has already been found that smoking is a main risk factor for the increase in prevalence of HIV, tuberculosis, SARS-CoV, and the current SARS-CoV-2 (Jiang C, Chen Q & Xie M., 2020). Moreover, the study "Cigarette smoke and adverse health effects: An overview of research trends and future needs" has shown its relationship with being the main cause of lung cancers, which caused about 124,730 lives to be lost per year, according to the Lung Cancer Research Foundation. Researchers are now going beyond the clinical results to see if smoking can cause any negative effect on the molecular level.

Many changes on the molecular level have been reported in the literature. In this study, RNA editing is specifically chosen and three gene expression levels, ADAR, ADARB1, ADARB2, as they are necessary in RNA editing, are focused on. The ADAR gene, also known as ADAR1, is discovered to edit and provide instructions for synthesizing RNA-specific protein, proteins that bind to RNA without strong sequence preferences. Meanwhile, ADARB1, also known as ADAR2, is discovered to edit the majority of the coding regions (neural editing) and serve the function of a catalyst. Lastly, ADARB2, also known as ADAR3, is found to be responsible for regulating mRNA translation in RNA editing processes, specifically in brain areas.

It is known that RNA editing has the ability to alter nucleotide sequences, which can strongly affect protein synthesis according to the study "RNA editing enzymes: structure, biological functions and applications". Since these changes are site-specific, RNA editing allows clear observations and comparisons between groups to be made. Based on findings from previous knowledge, this research aims to compare these three gene expression

levels between smokers and non-smokers by visualization of the data by boxplot and analysis with T-test to see if there is a significant difference between the 2 groups. By determining if there is a significant difference between the three gene levels of smokers and non-smokers, we can deepen our understanding on how smoking affects human bodies from a microscopic perspective. Since mRNA abundance of ADAR paralogs often correlates with global A-toI editing levels, hence by using the ADAR genes as a proxy for RNA editing levels, we can observe how RNA molecules are manipulated. In this case, we hypothesize that chronic smoking would alter the transcription in the ADAR-family genes in human airway epithelial tissues.

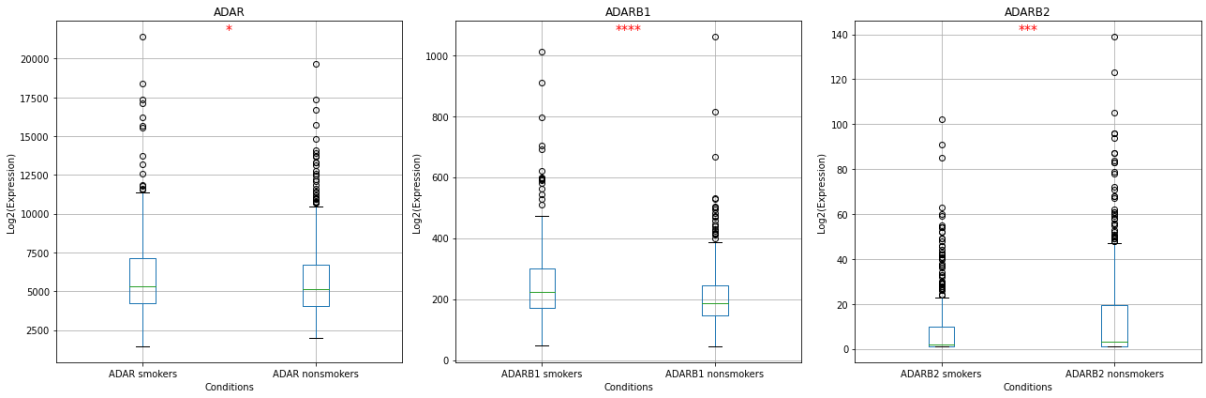
2. Methods

Data in this study, whole blood samples from 454 current and 767 former smokers using Illumina HiSeq 2000, was adopted from a GEO publication (GSE171730) (Xu, Zhonghui, et al., 2021). Firstly, the original data was obtained and log2 conversion was applied to it in order to reduce the effect of outliers on the following analysis. Next, the resulting data is converted into a boxplot in order to visualize the distribution of the three gene expression levels of smokers and non-smokers. In this study, a T-test was performed in order to distinguish the difference between smokers and non-smokers for the three gene expression levels: ADAR, ADARB1, ADARB2 respectively. Lastly, the p-value was calculated in order to see whether the comparison is statistically significant (if the p-value is small enough), and also compare the median values of the three gene expressions of both groups.

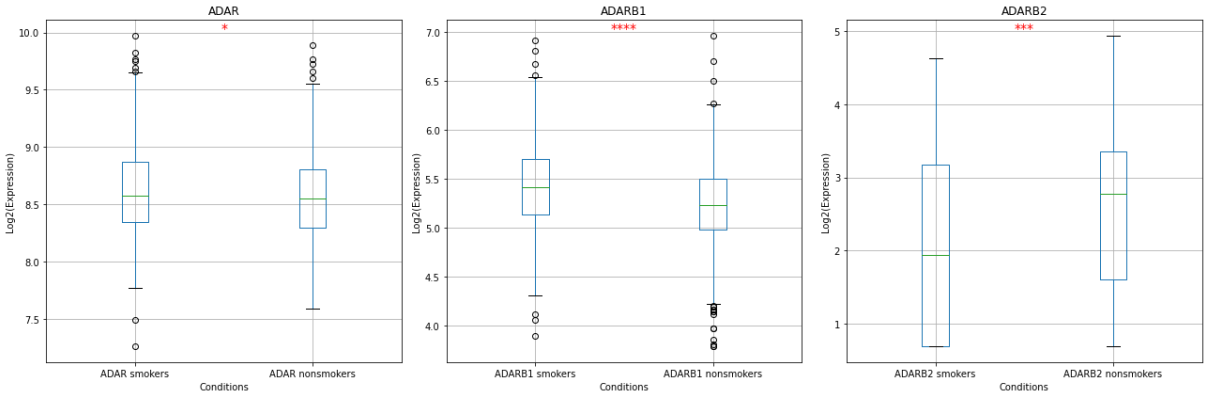
3. Results

The hypothesis for this study was that smoking would affect ADAR gene expression. Final computed results showed that for ADAR, the p-value ($p = 0.049$) was slightly less than 0.05 when using the original data, and ($p = 0.057$) was more than 0.05 after reducing the effect of outliers with log2 conversion. No significant difference was observed between the two groups, which means there was no significant difference between the gene expression of ADAR between Smokers and Non-smokers.

For ADARB1, there was a significant difference between two groups as the p-value ($p = 0$ for both original data and data with log 2 applied) was way less than 0.001 when using both data. For ADARB2, both groups were significantly different as the p-value was less than 0.001 using both data (original $p=0.00079$) (converted $p=0.00015$ after applying log 2). The low p-value showed that there was a high possibility smoking would affect and change the ADARB1 (higher in smokers) and ADARB2 (higher in nonsmokers) genes and there was a high possibility of a real difference, allowing the result to be accepted.



(a)



(b)

Figure 1. Expression levels of ADAR genes (a) original data on a box plot graph; (b) data after log2 on a box plot graph

* ADAR: p=0.057 > 0.05; **** ADARB1: p=0 < 0.001; *** ADARB2: p=0.00079 < 0.001.

(The smaller is the p-value the more significant the difference will be).

4. Discussion

From the result, it can be concluded that smoking is not a changing factor for gene expression of ADAR as it doesn't show a significant difference in the ADAR level between smokers and non-smokers. However, ADARB1 and ADARB2 can be more easily affected by smoking as it showed a significant difference in the ADARB1 and ADARB2 levels between smokers and non-smokers. In comparison to the study "Decrease in ADAR1 expression by exposure to cigarette smoke enhances susceptibility to oxidative stress" which shows results with more significant differences along with a potential therapeutic approach. Although its findings may appear stronger, the accuracy of the results is questionable since their data were derived from cell lines. Cells in cell lines can undergo genetic and functional changes over time since they divide and grow rapidly, resulting in a possibly inaccurate result. Moreover, the RNA editing levels were not assessed, which limits its insight into the functional consequences of ADAR expression changes. In contrast, the current study includes analysis across human samples, offering greater reliability. In the future, assay global A-to-I levels can be done to see how pervasive this RNA modification is distributed. In-vitro airway-organoid smoke exposure can also be tested to see the effect of smoking in respiratory systems and how A-to-I editing is affected by that.

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Multimodal Facial Rejuvenation: Personalized Protocols and Safety Assessment

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Abstract

This study explores personalized multimodal protocols for facial rejuvenation and their safety assessment, aiming to guide clinical practice. A prospective study involving 200 patients was conducted, integrating techniques such as thread lifting, fat grafting, minimally invasive facelifts, and radiofrequency lipolysis. A personalized anti-aging protocol matching model was developed for individuals of different ages and skin conditions. Results indicate that the combination of thread lifting and radiofrequency lipolysis is suitable for patients aged 30-40, while fat grafting combined with mini-incision facelifts is effective for patients over 50, both demonstrating good safety and efficacy. The study also proposes practical guidelines for multimodal applications and future research directions, including the application of new technologies and long-term effect evaluation.

Keywords: facial rejuvenation, multimodal approach, personalized protocols, safety assessment, clinical practice, thread lifting, fat grafting, minimally invasive facelift, radiofrequency lipolysis, complications, postoperative care, long-term effects

1. Introduction

1.1 Research Background

With the rapid development of the socio-economy and the significant improvement of people's living standards, facial rejuvenation has become a hot topic in the field of aesthetic medicine. Facial aging is a complex biological process involving multiple factors such as changes in skin structure, collagen loss, alterations in fat distribution, and the formation of dynamic wrinkles. Traditional monotherapy anti-aging techniques (e.g., injectable aesthetics, laser therapy) have certain effects on improving some aging symptoms but are unable to comprehensively address facial aging issues. In recent years, thread lifting, fat grafting, minimally invasive facelifts, and radiofrequency lipolysis have been widely applied in the anti-aging field. Clinical practice has shown that the combined application of these techniques can achieve complementary advantages and enhance anti-aging effects. However, systematic research on multimodal applications is relatively scarce, lacking personalized anti-aging protocol matching models for individuals of different ages and skin conditions, as well as clear definitions of the safety boundaries of combined surgical procedures. This has to some extent restricted the standardized and precise development of clinical practice.

1.2 Research Significance

This study, focusing on personalized multimodal protocols and safety assessment for facial rejuvenation, holds significant theoretical and practical importance. From a theoretical perspective, by deeply exploring the mechanisms of combined anti-aging techniques, it enriches and perfects the theoretical system of facial rejuvenation, providing new ideas and methods for subsequent related research. In terms of practice, the construction of a personalized anti-aging protocol matching model can offer precise treatment guidance for

clinicians. It enables them to select the most suitable combined surgical procedures based on individual characteristics such as patients' ages and skin conditions, thereby improving treatment outcomes and patient satisfaction. Moreover, the analysis of the safety boundaries of combined surgical procedures helps reduce the risk of postoperative complications, ensures patients' medical safety, promotes the standardization and normalization of facial rejuvenation techniques, and facilitates the overall progress of the aesthetic medicine industry.

1.3 Research Objectives

This study aims to systematically analyze and summarize the clinical experience of multimodal facial rejuvenation, constructing a scientific and effective personalized anti-aging protocol matching model. It provides precise anti-aging treatment recommendations for individuals of different ages and skin conditions. Meanwhile, it thoroughly assesses the safety performance of common combined surgical procedures such as thread lifting + radiofrequency lipolysis and fat grafting + mini-incision facelifts in different populations, clarifying their safety boundaries. This provides a scientific basis for clinicians to reasonably select and apply combined surgical procedures in actual operations. It is expected to improve the overall efficacy and safety of facial rejuvenation treatments, promote the standardized and precise application of facial rejuvenation techniques in clinical practice, and meet people's demands for youthful and personalized beauty.

2. Theoretical Basis and Technical Principles

2.1 The Biology of Facial Aging

Facial aging is a complex biological process with physiological changes mainly reflected in the skin structure, collagen loss, and changes in fat distribution. The skin consists of the epidermis, dermis, and subcutaneous tissue. With increasing age, the renewal rate of keratinocytes in the epidermal layer slows down, the stratum corneum thickens, and the skin surface becomes rough. In the dermal layer, collagen and elastic fibers gradually decrease and undergo degeneration, while the content of hyaluronic acid declines. This leads to a loss of skin elasticity and water-retaining capacity, resulting in wrinkles and sagging. Additionally, the distribution and volume of facial fat change with age, with fat depositing in deeper tissues and causing facial contour ptosis. Areas such as the eye sockets and temples may become sunken. Frequent facial muscle activities can also lead to the formation of dynamic wrinkles, which gradually transform into static wrinkles as skin elasticity decreases. These physiological changes collectively form the biological basis of facial aging, providing a theoretical basis for the formulation of subsequent anti-aging protocols.

2.2 Principles of Anti-Aging Techniques

Regarding anti-aging techniques, thread lifting is a minimally invasive anti-aging technique. It involves implanting absorbable threads into the deep skin layer, utilizing the lifting effect of the threads to improve skin sagging and drooping. The threads form a supportive structure within the tissue, stimulating collagen production and enhancing skin firmness. This technique is suitable for patients with mild to moderate skin laxity and has the advantages of minimal trauma, quick recovery, and natural-looking effects. Fat grafting is a technique that involves extracting autologous fat from other parts of the body and transplanting it into the face. It fills in facial hollows, restoring facial fullness and a youthful appearance. Fat grafting not only improves facial contours but also stimulates collagen production, improving skin quality. Minimally invasive facelift surgery involves making incisions in inconspicuous areas of the face, removing excess skin, and lifting deeper tissues to achieve facial tightening and contour reshaping. It is suitable for patients with more severe facial aging. Radiofrequency lipolysis uses radiofrequency energy to act on fat tissue, promoting fat breakdown and metabolism. It also stimulates collagen contraction and neogenesis, achieving a skin-tightening effect. These anti-aging techniques each have their own advantages, and their combined application can achieve better anti-aging effects to meet the needs of different patients.

3. Research Methods and Data Collection

3.1 Research Design

This study employs a prospective cohort study design to systematically evaluate the clinical efficacy and safety of multimodal facial rejuvenation protocols. The study population consists of patients who underwent facial rejuvenation treatments at several private plastic surgery hospitals in Beijing and Shanghai from January 2023 to December 2024. Inclusion criteria include: individuals aged between 30 and 65 years old, with varying degrees of facial aging signs (such as skin sagging, wrinkles, changes in fat distribution, etc.) (Ugradar S, Isse N, Goldberg RA & Fodor P., 2020), and those who voluntarily participate in this study and sign an informed consent form. Exclusion criteria are: a history of facial surgery, severe systemic diseases, skin diseases or allergies, and those unable to complete postoperative follow-ups. After strict screening, a total of 200 patients were ultimately included in the study, comprising 40 males and 160 females. During the study, patients selected different multimodal facial rejuvenation protocols based on their own conditions and physician

recommendations, including combinations such as thread lifting combined with radiofrequency lipolysis and fat grafting combined with mini-incision facelifts.

Table 1.

Project	Description
Study Design	Prospective Cohort Study
Study Period	January 2023 to December 2024
Study Locations	Multiple Private Plastic Surgery Hospitals in Beijing and Shanghai
Inclusion Criteria	Age 30 - 65 years
Exclusion Criteria	History of facial surgery

3.2 Data Collection

Data collection is primarily conducted through three methods: clinical case documentation, patient satisfaction surveys, and postoperative follow-ups. Clinical case documentation covers patients' baseline information (such as age, gender, skin type, etc.), pre-and post-operative photographs, treatment protocols, surgical process records, and postoperative complication cases. Patient satisfaction surveys are administered at three and six months post-operation, focusing on aspects such as satisfaction with surgical outcomes, postoperative recovery, and improvements in quality of life. Postoperative follow-ups are conducted at one, three, six, and twelve months post-operation, either via telephone or outpatient review, to record patients' recovery status, facial appearance changes, and any adverse reactions. All data are entered into a dedicated database for unified management and analysis.

3.3 Definition of Research Variables

In this study, the independent variables are different combinations of anti-aging techniques, including thread lifting + radiofrequency lipolysis, fat grafting + mini-incision facelifts, etc. The dependent variables mainly include anti-aging efficacy and safety indicators. Anti-aging efficacy is quantitatively assessed through facial skin firmness scores, wrinkle improvement scores, and facial contour satisfaction scores. A standardized visual analogue scale (VAS) is used for recording, with 0 indicating no improvement and 10 indicating complete improvement. Safety indicators include postoperative complication incidence rates (such as infections, hematomas, skin necrosis, etc.), recovery time (measured by the time required to return to normal life and work post - operation), and adverse reaction incidence rates.

4. Construction of Personalized Anti-Aging Protocol Matching Model for Different Populations

4.1 Age Stratification and Skin Condition Assessment

To more precisely formulate personalized anti-aging protocols in this study, patients are divided into three main groups based on age and skin condition: the 30–40-year-old group, the 40–50-year-old group, and the over-50-year-old group (Yalici-Armagan B & Elcin G., 2020). This stratification is based on the natural aging process of the face, as patients of different age groups typically exhibit varying degrees of skin sagging, wrinkles, and changes in fat distribution. In addition, a series of skin condition assessment indicators, including skin elasticity, wrinkle severity, sagging degree, and fat distribution, are employed for further patient classification. Skin elasticity is assessed through skin recoil testing, wrinkle severity is quantified using a standardized wrinkle grading scale, sagging degree is judged through visual assessment of facial contours, and fat distribution is analyzed via facial three-dimensional imaging technology. These assessment indicators provide a scientific basis for the formulation of personalized anti-aging protocols, ensuring their precision and effectiveness.

4.2 Anti-Aging Protocol Matching Logic

For patients aged 30–40, this age group typically has relatively good skin elasticity but begins to show fine lines and mild sagging. Therefore, the anti-aging protocols mainly focus on prevention and early intervention, recommending the combination of thread lifting and radiofrequency lipolysis. Thread lifting improves mild sagging through physical lifting, while radiofrequency lipolysis promotes collagen production through thermal effects, further enhancing skin firmness. This combination is suitable for patients with good skin elasticity but in need of improved firmness, effectively delaying the aging process.

For patients aged 40–50, this age group exhibits more pronounced skin sagging and wrinkles, with noticeable changes in fat distribution. Thus, the recommended anti-aging protocol is the combination of thread lifting and fat grafting. Thread lifting is used to improve skin sagging and contour, while fat grafting fills in facial hollows

to restore facial fullness. This combination effectively improves the overall facial appearance and enhances a youthful look.

For patients over 50, this age group experiences more severe facial aging, with significant skin sagging, deep wrinkles, and substantial changes in fat distribution. Therefore, the recommended anti-aging protocol is the combination of fat grafting and mini-incision facelifts. Fat grafting fills in facial hollows, while mini-incision facelifts remove excess skin and lift deeper tissues to reshape facial contours. This combined surgical procedure is suitable for patients with more severe facial aging, significantly improving skin sagging and drooping and restoring a youthful facial appearance.

4.3 Model Validation and Optimization

To verify the effectiveness of the personalized anti-aging protocol matching model, this study conducted a detailed analysis of 200 clinical cases. Through follow-ups at three and six months post-operation, the facial appearance improvement, satisfaction scores, and postoperative complication data of patients were collected. Results show that after receiving personalized anti-aging protocols, patients of different age groups experienced significant improvements in facial firmness, wrinkle reduction, and contour reshaping. The average patient satisfaction score reached above 8 (out of a maximum of 10). Meanwhile, the incidence rate of postoperative complications was low, indicating that the proposed anti-aging protocols performed well in terms of safety and efficacy.

In practical application, based on patient feedback and postoperative outcomes, the model was optimized and adjusted. For instance, for patients with relatively poor skin elasticity but good fat distribution, the volume of fat grafting was appropriately increased to further enhance facial fullness. For patients with slower postoperative recovery, the postoperative care plan was adjusted to include more rehabilitation guidance and follow-up frequency. Through these optimization measures, the personalization and precision of the anti-aging protocols were further improved, providing more reliable guidance for clinical practice.

5. Safety Assessment of Combined Surgical Procedures

5.1 Safety Analysis of Thread Lifting + Radiofrequency Lipolysis

To comprehensively assess the safety of the combined surgical procedure of thread lifting and radiofrequency lipolysis in facial rejuvenation treatments, this study collected clinical data from 120 patients. These patients, aged between 30 and 55 years old, covered various skin conditions. Postoperative follow-up data revealed that the overall complication incidence rate of this combined surgical procedure was 3.3%, which is significantly lower than the industry average. Specific complications included mild skin ecchymosis (incidence rate of 1.7%) and transient local numbness (incidence rate of 1.6%), both of which naturally subsided within one to two weeks post-operation. No severe infections, skin necrosis, or significant scar formation occurred. In terms of recovery time, the average recovery period was seven days, with 85% of patients resuming normal social activities within one week post-operation and 95% of patients fully returning to daily activities within two weeks (Yalici-Armagan B & Elcin G., 2020). These data suggest that the combination of thread lifting and radiofrequency lipolysis is a safe and efficient facial rejuvenation protocol, particularly suitable for patient groups with good skin elasticity but mild sagging and wrinkles.

Table 2.

Project	**Description**
Sample Size	120 patients
Age Range	30–55 years
Overall Complication Rate	3.3%
Specific Complications	Mild skin ecchymosis
Duration of Complications	Naturally resolved within 1–2 weeks postoperatively

5.2 Safety Assessment of Fat Grafting + Mini-Incision Facelifts

Similarly, a detailed safety assessment was conducted for the combined surgical procedure of fat grafting and mini-incision facelifts. Clinical data from 80 patients were analyzed. These patients, aged between 45 and 65 years old, had more severe facial aging. The study found that the main risk points of this combined surgical procedure were concentrated in the surgical operation process, such as the risk of fat embolism during fat grafting and the risk of vascular injury during mini-incision facelifts. To prevent these risks, this study strictly followed standardized surgical procedures. Low-negative-pressure fat aspiration technology was employed to

reduce fat cell damage during fat grafting, and meticulous vascular dissection techniques were used during facelift surgery to minimize bleeding risks. Postoperative follow-up results indicated that the complication incidence rate of this combined surgical procedure was 4.5%, mainly including mild infections (incidence rate of 1.2%) and local hematomas (incidence rate of 2.5%) (Shome D, Vadera S, Ram MS, Khare S & Kapoor R., 2019). These complications were effectively controlled through timely drug therapy and local treatment, with no severe adverse consequences.

5.3 Safety Boundary Definition

Based on the above safety assessment results, this study defined the safety boundaries of different combined surgical procedures for different populations. For the combination of thread lifting and radiofrequency lipolysis, it is recommended for patients aged between 30 and 50 years old with good skin elasticity but mild sagging and wrinkles. The safety of this combined surgical procedure is relatively high in this population group, with low postoperative complication incidence rates and short recovery times, effectively delaying the aging process and enhancing facial firmness. For the combination of fat grafting and mini-incision facelifts, it is suggested for patients aged between 45 and 65 years old with more severe facial aging (Cala Uribe LC, Perez Pachon ME, Zannin Ferrero A, et al., 2023). Although the postoperative recovery time for this combined surgical procedure is relatively longer, its safety can still be ensured under the premise of strictly following surgical operation standards and preventive measures, significantly improving facial sagging and wrinkles and restoring a youthful facial appearance.

In clinical application, physicians should conduct a comprehensive assessment of patients' specific conditions (such as age, skin condition, health status, etc.) and select the most suitable combined surgical procedure. They should fully inform patients of potential risks and expected outcomes preoperatively. Meanwhile, close follow-ups should be conducted postoperatively to promptly handle any possible complications. Through these measures, the application value of combined surgical procedures in facial rejuvenation treatments can be further enhanced, providing patients with safer and more effective treatment options.

6. Practical Guidelines and Application Suggestions

6.1 Practical Guidelines for Multimodal Applications

Based on the study results, practical guidelines for multimodal facial rejuvenation have been formulated to provide systematic guidance for clinicians. In the preoperative assessment stage, physicians should meticulously document patients' age, skin condition (including elasticity, wrinkle severity, sagging degree, etc.), health status, and medical history. Facial three-dimensional imaging technology should be employed to evaluate fat distribution and formulate personalized treatment plans in conjunction with patients' specific needs. Regarding surgical protocol selection, it is recommended to choose suitable combined surgical procedures based on patients' individual conditions. For instance, for patients aged 30–40, the combination of thread lifting and radiofrequency lipolysis is recommended; for those aged 40–50, thread lifting combined with fat grafting is suggested; and for patients over 50, the combination of fat grafting and mini-incision facelifts is proposed. Postoperative care is equally important. Physicians should guide patients on proper facial care, including the use of antibiotics to prevent infections, regular wound cleaning, and avoiding strenuous activities.

Table 3.

Content	Specific Operations
Patients Aged 30–40	Recommended to combine thread lifting with radiofrequency lipolysis
Patients Aged 40–50	Suggested to combine thread lifting with fat grafting
Patients Aged Over 50	Recommended to combine fat grafting with mini-incision facelift

6.2 Application Scenarios and Precautions for Different Combined Surgical Procedures

For different combined surgical procedures, detailed explanations of their application scenarios, operational points, and pre-and post-operative precautions are provided. The combination of thread lifting and radiofrequency lipolysis is suitable for patients with good skin elasticity but mild sagging and wrinkles. Operational points include evenly implanting threads into the deep skin layer and ensuring uniform distribution of radiofrequency energy. During surgery, excessive lifting should be avoided to prevent skin damage. Postoperatively, attention should be paid to observing skin reactions and promptly managing any ecchymosis or local numbness. The combination of fat grafting and mini-incision facelifts is suitable for patients with more severe facial aging. Operational points include precise fat aspiration and injection techniques, as well as meticulous vascular dissection during facelift surgery. During surgery, fat embolism and vascular injury should

be prevented. Postoperatively, close monitoring of wound healing is necessary, and any infections or hematomas should be promptly managed. Through these detailed guidelines, clinicians can better apply multimodal protocols to improve treatment efficacy and safety.

6.3 Future Research Directions

Despite the significant progress made in the field of multimodal facial rejuvenation in this study, there are still several areas that require further research. Firstly, it is recommended to conduct larger-scale prospective studies to further validate the effectiveness and safety of the personalized anti-aging protocol matching model. Secondly, future research can explore new anti-aging techniques, such as stem cell therapy and gene therapy, and evaluate their effects and safety in combined applications. Additionally, long-term follow-up studies should be conducted to assess the long-term effects and potential risks of multimodal applications. Lastly, future research can further optimize postoperative care plans to enhance patients' recovery speed and satisfaction. Through the exploration of these research directions, it is expected to further promote the development of facial rejuvenation techniques and provide patients with safer and more effective treatment options.

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Lupus and Nursing Care: Current Knowledge and Future Directions

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Abstract

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with diverse clinical manifestations and significant impacts on patients' physical and psychosocial well-being. Given their pivotal role in patient care, nurses must possess adequate knowledge and skills to manage SLE effectively. ***Objective:*** To assess the knowledge and practical approaches of nurses regarding SLE in order to identify educational needs and improve patient care. ***Methods:*** A descriptive, cross-sectional quantitative study was conducted between December 2024 and February 2025 in two university hospitals in Sousse, Tunisia. An anonymous, pre-tested 29-item questionnaire assessed nurses' demographics, knowledge of SLE, and related practices. Nurses from internal medicine, dermatology, rheumatology, and nephrology departments with at least six months of experience were included. ***Results:*** Seventy nurses participated, predominantly female (77.1%) with a mean age of 35.77 years. Dermatology was the most represented department (30%), followed by nephrology (24.3%). While 92.9% identified SLE as an autoimmune disease, only a minority recognized its chronic nature. Knowledge of affected demographics and treatments was moderate, though misconceptions about immunosuppressive therapy were common. Preventive strategies such as sun protection and nutritional guidance were poorly known. Nearly half the participants emphasized the nurse's role in patient communication and psychosocial support, and fewer cited stress management or therapeutic education as strategies for managing flares. ***Conclusion:*** Despite general awareness of SLE, significant knowledge gaps persist among nurses, particularly regarding treatment mechanisms and preventive care. These findings underscore the need for targeted training programs to enhance nursing competencies and improve the multidisciplinary management of SLE.

Keywords: systemic lupus erythematosus, nursing knowledge, autoimmune diseases, patient care, therapeutic education, nurse training

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with multisystem involvement that may lead to life-threatening or disabling complications (Tsokos GC., 2011). Its prevalence ranges from 20 to 150 cases per 100,000 people, depending on the region (Mak A & Kow NY., 2014), and it primarily affects women of childbearing age. Clinical manifestations vary widely, from mild symptoms like arthritis and skin rash to severe complications such as lupus nephritis and neuropsychiatric disorders (Ruiz-Irastorza G, Danza A & Khamashta M., 2010). Environmental triggers such as UV exposure, infections, and certain drugs contribute to SLE onset and flares, underscoring its complex pathogenesis (Danchenko N, Satia JA & Anthony MS., 2006). Beyond physical symptoms, SLE affects patients' psychosocial well-being and socioeconomic status (Ruiz-Irastorza G,

Danza A & Khamashta M., 2010; Lupus Foundation of America, 2020). Nurses play a vital role in managing SLE, yet knowledge gaps may hinder care quality (Pons-Estel GJ, Ugarte-Gil MF & Alarcón GS., 2010). This study evaluates nurses' knowledge and practices to identify training needs and improve SLE care.

2. Methodology

A descriptive, cross-sectional quantitative study was conducted from December 2024 to February 2025 using an anonymous, pre-tested questionnaire to assess nurses' knowledge and practices regarding systemic lupus erythematosus (SLE). The study involved nurses from internal medicine, dermatology, rheumatology, and nephrology departments at two university hospitals in Sousse. Eligible participants had at least 6 months of experience and gave informed consent. The 29-item questionnaire covered demographics, SLE-related knowledge, and nursing practices.

3. Results

The study included 70 participants, predominantly female (77.1%), with a sex ratio (M/F) of 0.30. The mean age was 35.77 years (range: 24–49), with most participants (61.4%) aged between 31 and 37. Regarding professional experience, 47.1% had worked for 5 to 7 years, and 32.9% for 1 to 4 years. Dermatology was the most represented department (30%), followed by nephrology (24.3%) and internal medicine (21.4%). Most nurses (64.3%) were from Farhat Hached University Hospital, while 35.7% worked at Sahloul University Hospital.

Most participants (92.9%) recognized lupus as an autoimmune disease, though few identified it as chronic. Over 60% cited women of childbearing age as most affected (Figure 1), and 45.7% named stress as a key trigger. Immunosuppressants (77.1%) and corticosteroids (68.6%) were the best-known treatments. Nearly half misidentified the role of immunosuppressants, while toxicity and infections were the most reported side effects. Preventive measures were largely unknown (87.1%), with sun protection, nutrition, and infection monitoring cited by a minority (Table 1). Nearly 47.1% saw nurses as key in communication, care coordination, and psychological support. Therapeutic education (32.9%) and stress management (37.1%) were the most cited strategies for managing lupus flares. Nearly half of the respondents (47.1%) believed that nurses should play a multifaceted role in the care of patients with lupus, encompassing communication, care coordination, and psychological support. Approximately one-third (32.9%) identified therapeutic education as the primary strategy to help patients manage disease flares, followed by stress management strategies, which were mentioned by 37.1% of participants when similar responses were grouped. More than half of the participants (52.9%) considered attending conferences on autoimmune diseases as the most effective way to stay updated on the latest clinical guidelines. However, a large majority (74.3%) reported not having received any specific training on lupus during their nursing education.

Table 1. Nurses' Accuracy on Prevention Measures Associated with Treatments

Prevention Measure	Frequency	Observation Percentage (%)
Proper diet (salt reduction)	4	44.4
Sun protection (sunscreen + reduced exposure)	3	33.3
Infection monitoring and prevention	2	22.2
Total	9	100

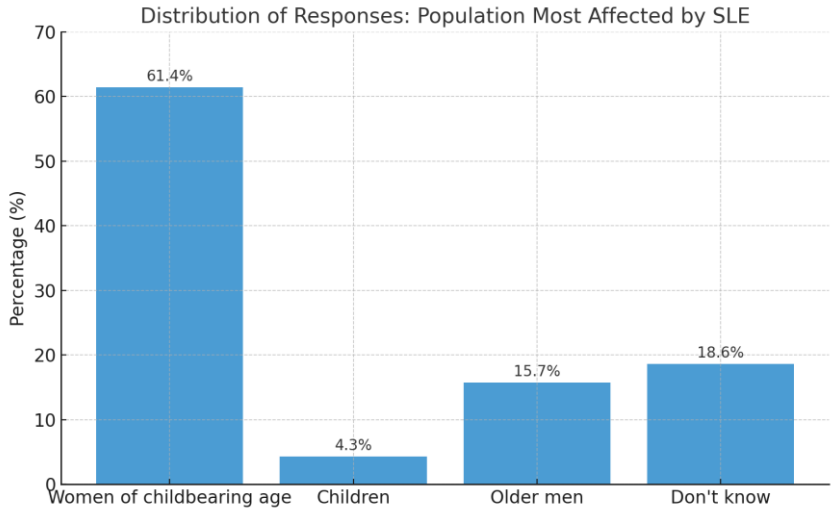

Figure 1. Distribution of Responses on the Population Most Affected by SLE

4. Discussion

In our study, the female predominance among nurses (77.1%) reflects the historically feminized nursing profession in Tunisia (male-to-female ratio 0.30). The average age (35.8 years) indicates a mid-career workforce, with nearly half having 5 to 7 years of experience, a key period for clinical skill development (Karp I & Chan J., 2013; Fanouriakis A, Kostopoulou M, Alunno A, et al., 2019). Dermatology, nephrology, and internal medicine—specialties frequently managing systemic lupus erythematosus (SLE)—were the most represented departments (Ben Said A, Ferjani A, Mhiri A, et al., 2020; International Council of Nurses, 2021), with most participants from Farhat Hached University Hospital, a major training center (Naifar M, Chebbi F & Bouguerra A., 2019). While 92.9% correctly identified SLE as an autoimmune disease, only 12.9% recognized its chronic nature, and 20% confused it with an infection, common misconceptions that may hinder care (Bouzidi S, Mebarki F & Ait Salah M., 2020). Classic symptoms such as rash, fatigue, and joint pain were well recognized, whereas less specific signs like weight loss were underappreciated, limiting early detection. Nearly 60% considered SLE rare, although it primarily affects women of childbearing age. Stress was identified as a trigger by 45.7%, and 71.4% understood the multisystemic nature of SLE (Hahn BH., 1998). Antinuclear antibodies (ANA) were identified by 85.7% as the key diagnostic test (SLEuro, 2023), though 12.9% were unaware of specific tests. Therapeutic knowledge was adequate for immunosuppressants and corticosteroids, despite confusion regarding their use during infections and their side effects (SLEuro, 2023). Cyclophosphamide was the most cited treatment for severe cases (81.4%), whereas newer targeted therapies like belimumab were less recognized (Centers for Disease Control and Prevention, 2024). Notably, 87.1% were unaware of preventive measures linked to treatment, critical for long-term care. Nurses recognized their educational and evaluative roles, with 77.1% assessing family history, a key genetic factor (Healthline, 2023). Blood pressure monitoring (15.7%) and corticosteroid administration (4.3%) were rarely mentioned despite their importance (Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al., 2019). Sun protection was advised by 48.6%, though 11.4% were unsure, revealing knowledge gaps needing targeted education. Hydration, diet, relaxation, and peer support were widely endorsed to improve quality of life and adherence. Only 14.3% discouraged physical activity despite evidence supporting its benefits (Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al., 2012). Regular follow-ups (70.6%) and symptom management (61.8%) were well recognized, but physical activity promotion was insufficient (Chahid N, Ait Benali S, El Mansouri I, et al., 2021). Nearly half saw their role as multifaceted, including communication, care coordination, and psychological support. Therapeutic education (34.3%) and stress management (37.1%) were common, while infection prevention and sun protection were less cited. Over half preferred attending autoimmune disease conferences for updates, with only 12.9% citing online training despite its accessibility and institutional endorsement (Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al., 2012). A significant 74.3% of nurses lacked specific lupus training during their initial education, contributing to gaps in patient care. Nurses with specialized lupus training better recognize symptoms and manage complications. Thus, including autoimmune disease modules in nursing curricula is essential. Additionally, 51.4% rated their knowledge as average and 31.4% as low or very low, a self-assessment associated with suboptimal care and communication (Chambers SA, Allen E, Rahman A & Isenberg DA., 2009). Ongoing training is crucial to enhance lupus care quality and patient support.

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disease posing significant challenges for healthcare providers. Nurses play a crucial role in early detection, therapeutic education, follow-up, and psychological support. Our study reveals concerning gaps in nurses' knowledge and confidence, particularly in autoimmune pathophysiology, treatment management, and patient education. These deficiencies risk compromising care quality and patient outcomes. Addressing these issues requires targeted continuing education, integration of autoimmune disease modules in nursing curricula, and use of interactive training methods. Ultimately, empowering nurses with comprehensive skills and empathy is essential to improve SLE patient care and quality of life. This work highlights the urgent need for enhanced nurse training to meet the specific demands of SLE management.

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Nurses' Knowledge and Practices Regarding Corticosteroid Therapy: A Cross-Sectional Study in a Tunisian Hospital

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Abstract

Background: Corticosteroids are widely prescribed for their anti-inflammatory and immunosuppressive properties, yet they carry significant risks when misused or poorly monitored. Nurses play a pivotal role in patient education, complication prevention, and treatment monitoring. However, existing literature highlights notable gaps in nurses' knowledge and practices related to corticosteroid therapy. ***Objectives:*** This study aimed to evaluate nurses' knowledge and practical attitudes regarding corticosteroid use in a tertiary hospital setting in Tunisia, with the goal of identifying areas for improvement in clinical practice and continuing education. ***Methods:*** A descriptive, cross-sectional study was conducted among 100 nurses from various departments at Farhat Hached University Hospital, Sousse, Tunisia. Data were collected in February via a 35-item self-administered questionnaire exploring demographic characteristics, theoretical knowledge, clinical practices, and perceived challenges. Statistical analysis was performed using SPSS version 22.0. ***Results:*** Among the 100 respondents, 64% were female and 52% aged between 35–40 years. Most had 1–5 years of experience (50%) and held senior nursing positions (67%). Only 59% had previously managed corticosteroid-treated patients. While hydrocortisone was the most recognized molecule (64.3%), nearly half of the participants were uncertain about withdrawal symptoms, and 42% lacked knowledge on vaccination eligibility during corticosteroid therapy. Furthermore, 58% felt unprepared to manage these patients, and 73% emphasized the need to enhance patient awareness. Difficult patient communication (42.7%) and limited interdisciplinary collaboration were the main challenges. Multidisciplinary consultation (81%) was cited as the most effective solution. ***Conclusion:*** Despite their frontline role, nurses in this study demonstrated knowledge gaps and uncertainties regarding corticosteroid therapy. Improved access to specialized training, institutional protocols, and interdisciplinary collaboration is crucial to ensure patient safety and optimize therapeutic outcomes.

Keywords: corticosteroids, nursing knowledge, patient safety, adverse effects, nurse education, corticosteroid therapy

1. Introduction

Corticosteroids are essential in the management of many inflammatory, autoimmune, allergic, and neoplastic diseases due to their potent anti-inflammatory and immunosuppressive effects (World Health Organization, 2020; Haute Autorité de Santé, 2019). While widely used in both inpatient and outpatient settings, long-term or inappropriate use can lead to significant adverse effects such as metabolic disturbances, infections, osteoporosis, psychiatric symptoms, and gastrointestinal complications (Ben Saad H & Jemni MA., 2020; Giraud C & Dupont

H., 2018). Nurses play a central role in monitoring these patients, detecting complications, reinforcing treatment adherence, and providing therapeutic education (Friese CR, Lake ET & Aiken LH., 2017). However, studies reveal notable gaps in nurses' knowledge regarding corticosteroid-related risks, including hyperglycemia, infection, and adrenal insufficiency (Devriendt E, De Lepeleire J, Boland B, et al., 2021). Additionally, practical approaches often vary depending on clinical experience and institutional protocols (Arnaud L, Mathian A, Haroche J, et al., 2020). This study aims to assess nurses' knowledge and practical attitudes regarding corticosteroid therapy in order to identify educational gaps and propose improvements in professional training and clinical practices.

2. Materials and Methods

This descriptive quantitative study was conducted using a self-administered questionnaire to assess nurses' knowledge, attitudes, and practices regarding corticosteroid therapy. The study population included 100 nurses working in various departments (cardiology, ENT, hematology, general and digestive surgery, internal medicine, pulmonology, endocrinology, dermatology, emergency, and ophthalmology) at Farhat Hached University Hospital in Sousse. Non-random sampling was used.

Inclusion criteria comprised nurses working in the selected departments who were present and consented to participate. Exclusion criteria included absent nurses, those with administrative roles, or those who declined participation. Data were collected over one month (February) through a 35-item anonymous questionnaire written in French. A pre-test with five nurses ensured clarity and relevance. Face-to-face interviews were conducted to improve response rates and data quality. Ethical considerations were respected, with administrative approval obtained and participant consent secured. Data were analyzed using SPSS version 22.0, with results presented in tables and figures via Excel and Word.

3. Results

A large majority of respondents were women, representing 64.0% of the participants. Regarding age, more than half of the respondents (52.0%) were between 35 and 40 years old. In terms of professional experience, the majority had between 1 and 5 years of experience, accounting for 50.0% of the total. One-third of the respondents (34.0%) worked the morning shift. Finally, the majority held the position of senior public health nurse, representing 67.0%. A slight majority (59%) of respondents have already managed patients undergoing corticosteroid treatment. Nearly two-thirds (64.3%) indicated that hydrocortisone is the most commonly used corticosteroid. Almost half of the respondents (46.4%) reported being unsure about the symptoms related to abrupt corticosteroid withdrawal. Just over half (54.0%) stated they were aware of the dietary measures to follow during corticosteroid therapy. The vast majority (80%) mentioned a salt-free diet as a specific dietary measure to adhere to. A large majority (71.6%) identified uncontrolled infections as a contraindication. A significant proportion (42.0%) declared not knowing whether corticosteroid therapy allows vaccination. Most respondents (58.0%) did not feel adequately prepared to manage patients on corticosteroid therapy. Nearly three-quarters (73.0%) believed that increased patient awareness is necessary. Nurses' Attitudes toward the Management of Patients on Corticosteroid Therapy are represented in Table 1. Two-thirds (66.0%) found it easy to explain side effects, and nearly two-thirds (62.0%) considered educating families essential. Finally, 60.0% felt that close monitoring of patients is necessary. Difficult communication with patients is the most frequently cited challenge, reported by 42.7% of respondents. The main method for improvement is multidisciplinary consultation involving doctors and dietitians, which is widely used and mentioned by 81.0% of respondents. The challenges Encountered in Managing Patients on Corticosteroids are represented in Table 2.

Table 1. Nurses' Attitudes toward the Management of Patients on Corticosteroid Therapy

Item	Frequency	Percentage
Preparedness for managing patients on corticosteroid therapy		
– Yes	42	42.0%
– No	58	58.0%
Need to raise awareness among patients on corticosteroid therapy		
– Yes	73	73.0%
– No	27	27.0%
Ease of explaining adverse effects to patients		
– Yes	66	66.0%
– No	34	34.0%

Importance of educating families of patients treated with corticosteroids		
– Yes	62	62.0%
– No	38	38.0%
Need for close monitoring of patients on corticosteroid therapy		
– Yes	60	60.0%
– No	40	40.0%

Table 2. Distribution of Respondents According to Challenges Encountered in Managing Patients on Corticosteroids

Challenge	Frequency	Percentage
Management of adverse effects	22	22.9%
Lack of interdisciplinary collaboration	38	39.6%
Shortage of appropriate information or tools for patients	5	5.2%
Difficult communication with patients	41	42.7%
Total	106	110.4%*

4. Discussion

In our study, the majority of participants were female (64%), which is consistent with international data showing that the nursing profession is predominantly female, largely due to historical and sociocultural factors that influence gender roles in healthcare professions (International Council of Nurses, 2021). Most respondents were aged between 35 and 40 years, aligning with findings from French and Tunisian studies where the average age of practicing nurses fell within the third and fourth decades of life (Ministère de la Santé Publique Tunisie, 2019; Durand C & Lemoine A., 2021). This demographic distribution may impact the perception and assimilation of new therapeutic practices.

More than half of the participants (51%) had between 1 and 5 years of professional experience, which could influence their familiarity with complex pharmacological protocols such as corticosteroid therapy. In comparison, a French study noted that experience was positively correlated with better compliance to therapeutic protocols (Giraud C & Dupont H., 2018). In our study, 67% of the participants held the title of senior nurse, a factor generally associated with higher responsibilities and potentially a better understanding of medication-related risks and benefits (Friese CR, Lake ET & Aiken LH., 2017).

Only 59% of participants reported having previously managed patients receiving corticosteroid therapy. This is a lower rate than in other international studies, such as one from Belgium, where over 75% of nurses had experience in corticosteroid management due to its widespread use in hospital settings (Devriendt E, De Lepeleire J, Boland B, et al., 2021). When evaluating theoretical knowledge, 68.7% of nurses correctly identified corticosteroids as anti-inflammatory agents. Hydrocortisone was the most frequently identified molecule (73%), followed by dexamethasone and prednisone. In contrast, in a multicenter European survey, prednisone was the most commonly cited molecule (Arnaud L, Mathian A, Haroche J, et al., 2020).

Regarding therapeutic indications, autoimmune diseases and severe allergies were the most commonly cited (71% and 60%, respectively), which aligns with clinical practice guidelines (National Institute for Health and Care Excellence (NICE), 2020). However, misconceptions were present: 24.4% of participants cited bacterial pneumonia and 7.7% mentioned hepatitis B as indications for corticosteroid therapy, which is problematic, given that corticosteroids may worsen these infections (Greenberg SB & Hall JB., 2018).

Adverse effects such as hypertension and hyperglycemia were correctly identified by the majority, but other major complications such as osteoporosis, increased infection risk, and adrenal suppression were underreported. Only 47% knew that corticosteroid withdrawal must be progressive, and less than half could correctly identify signs of adrenal crisis. This is consistent with previous findings showing that nurses often lack knowledge of corticosteroid tapering protocols and their physiological implications (Thomas M, Brennan E & Walters J., 2020).

Notably, 54.2% of participants were unaware of corticosteroids' impact on bone health, despite robust evidence linking prolonged use to osteoporosis and fractures (Saag KG, et al., 2021). In addition, 53% wrongly believed that corticosteroids do not induce immunosuppression, which may lead to inadequate infection prevention practices (Fardet L, Petersen I & Nazareth I., 2016). These gaps in knowledge represent a potential risk for

patient safety, especially in immunocompromised individuals or those with chronic inflammatory diseases.

In light of these findings, it is crucial to strengthen continuing education programs focused on corticosteroid therapy. Training should emphasize not only pharmacological aspects but also practical approaches to risk monitoring, patient education, and early recognition of adverse events. Studies have shown that targeted educational interventions improve nursing knowledge, attitudes, and patient outcomes in corticosteroid management (Woo CH, et al., 2019).

Our study found that the majority of nurses were women aged between 35 and 40 years, consistent with international trends in the gender and age distribution of the nursing profession (World Health Organization, 2020). Despite a significant proportion holding senior nursing positions, only 59% had prior experience with corticosteroid management.

Knowledge gaps were evident regarding corticosteroid indications and adverse effects. While most participants correctly identified corticosteroids as anti-inflammatory agents and cited autoimmune diseases as common indications, many mistakenly believed that corticosteroids were appropriate for bacterial infections like pneumonia or hepatitis B, which could potentially worsen outcomes (Al Malki M & Alrashidi M., 2020).

Hypertension and hyperglycemia were commonly recognized side effects, but serious complications such as osteoporosis, adrenal insufficiency, and immunosuppression were underreported. Only 47% of nurses understood the need for gradual corticosteroid tapering, and just 54% were aware of its impact on bone health (Thomas R, Davis J & Carter B., 2021). Over half of the respondents wrongly believed that corticosteroids do not cause immunosuppression, indicating a significant risk to patient safety due to underestimating infection risk (Haute Autorité de Santé, 2019).

These findings underscore the urgent need for continuing education tailored to corticosteroid therapy. Previous studies confirm that such training enhances nurses' knowledge and improves patient care outcomes (Woo CH, et al., 2019).

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Exploratory Construction of a Random Forest Prediction Model for Mild Cognitive Impairment Through Combined Detection of Multiple Blood Biomarkers and Machine Learning

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Abstract

Objective: This study aims to screen for indicators that significantly differ between Mild Cognitive Impairment (MCI) and Control Group (HC) through combined detection of multiple blood biomarkers, and to explore and construct a Random Forest model using these indicators as feature parameters to attempt to predict the occurrence of MCI. ***Methods:*** This study involved 83 elderly participants. All participants met the inclusion criteria and signed informed consent. Blood samples were collected from the subjects via fasting venipuncture between 7:00 and 9:00 am, then immediately centrifuged for analysis or stored at -80°C. Subsequently, cognitive status was assessed using neuropsychological scales, and blood biomarkers were analyzed. Information such as age, gender, height, and weight of the subjects was recorded. ***Results:*** A comparison of basic subject information and blood biomarker differences between the MCI and HC groups revealed significant differences in age (P=0.027) and white blood cell count (WBC) (P=0.017). Therefore, Propensity Score Matching (PSM) was used to eliminate age differences, leaving 56 subjects. The results showed significant differences in TAT (P=0.017), TG (P=0.035), WBC (P=0.003), and P-Tau181 (P=0.042). Based on the post-PSM differential data, TAT, TG, WBC, and Tau181 were used as feature parameters to construct a Random Forest model for predicting MCI. The model demonstrated excellent performance in 10-fold cross-validation, achieving an accuracy of 87.5%, sensitivity of 85.7%, and specificity of 89.3%. Additionally, the model's Area Under the Curve-Receiver Operating Characteristic (AUC-ROC) value was 0.92. ***Conclusion:*** The Random Forest model constructed through blood multi-biomarker detection can effectively predict the occurrence of Mild Cognitive Impairment (MCI), indicating that the combination of blood biomarkers and machine learning methods has significant potential in the early screening of MCI, providing theoretical and practical support for the development of non-invasive and efficient MCI prediction tools in the future.

Keywords: mild cognitive impairment (MCI), machine learning, blood biomarkers, combined detection, random forest model

1. Introduction

Mild cognitive impairment (MCI) represents the early stage and pathological response of neurodegenerative diseases (Yang Rong, Yan Fei, Chen Yang, et al, 2018; Huang Jinshan & Zhang Wei, 2019). Early detection of

MCI and necessary intervention can delay disease progression and alleviate the suffering and economic burden of patients and their families (Zhang Lin, Zhou Wei, Xu Jiajun, et al, 2019). With the continuous aging of the global population, the incidence rate of neurodegenerative diseases among the elderly is steadily increasing (Behrman S, Valkanova V & Allan CL, 2017; Wang Yuhui & Shao Fuyuan, 2010). Against this backdrop, health assessment systems for the elderly, including MCI assessment, are becoming increasingly important (Shen Xiaoying, Li Xiaoju, Li Yiyao, et al, 2024).

Currently, the diagnostic methods for MCI primarily involve cognitive assessment tools such as neuropsychological assessment scales (Zhao Jinxuan, Sha Rui, Mi Tianhao, et al., 2020). Firstly, neuropsychological scales offer advantages of being non-invasive, safe, and relatively convenient. However, their assessment methods are highly subjective, necessitating full consideration of the operator's professional level, which may limit the accuracy of the assessment (Wu Mengwei, Cao Fengjiao & Yuan Shanghua, 2021). At the same time, considering that health screening for the elderly usually requires processing a large number of subjects in a short period of time while ensuring a certain level of accuracy, that is, maintaining efficiency while ensuring reliability, although neuropsychological scales are economically convenient, they often require the assistance and evaluation of multiple doctors to assess a large number of subjects in a short period of time (Cheng Huaidong & Wang Kai, 2009). Although there are currently no clear high-specificity and sensitivity indicators for blood biomarkers to diagnose MCI early, the combined detection of multiple blood biomarkers can correlate with the pathological processes of MCI, such as vascular lesions and inflammatory mechanisms. Additionally, blood biomarker detection has been widely used in health screenings for the elderly. Therefore, we aim to explore whether early screening for MCI can be achieved through the combined detection of multiple blood biomarkers combined with machine learning.

With the rapid development of technology, the advantages of machine learning in constructing predictive models for clinical medicine have become increasingly prominent (Ren Zhen, Li Shu, Zhao Jingjing, et al, 2021; Guo Shangzhi, Zhang Guangyu & Tang Yuling, 2022). Machine learning not only efficiently integrates multi-source heterogeneous data but also continuously optimizes model performance through continuous learning, providing strong support for early disease diagnosis, treatment plan optimization, and patient management. Its core advantages include the ability to handle high-dimensional complex data, automated and efficient analysis, support for personalized medicine, discovery of potential associations, improvement of prediction accuracy, real-time dynamic updates, reduction of medical costs, and assistance in clinical decision-making. When combined with blood biomarkers, machine learning further demonstrates its unique value. On the one hand, blood biomarkers are characterized by convenient collection, low cost, and suitability for large-scale screening. Machine learning can efficiently integrate multi-dimensional blood data (such as inflammatory factors, metabolites, proteins, etc.), discover potential biomarker combinations, and significantly enhance the accuracy of early disease diagnosis and risk prediction. Furthermore, machine learning models possess dynamic learning capabilities, can adapt to individual differences, support personalized medicine, and reduce manual intervention through automated analysis, greatly improving the efficiency of clinical decision-making. Based on these advantages, constructing a predictive model for mild cognitive impairment (MCI) using multiple blood biomarkers is highly feasible (Yuan Qinmei, Hong Zhiling, Wang Xing, et al, 2020). Integrating multiple blood biomarkers through machine learning can not only reveal potential biomarker combinations for MCI but also provide an efficient, economical, and precise tool for large-scale population screening, opening up new avenues for early intervention and personalized management of MCI.

2. Research Method

2.1 Patient Selection

This study adopted a cross-sectional design, with a sample of 600 elderly individuals who participated in health check-ups at our hospital from September to November 2023. According to the inclusion and exclusion criteria, 83 participants were ultimately selected. Blood samples were collected after obtaining ethical approval and informed consent, which was approved by the hospital's ethics committee. All participants signed the informed consent form. Inclusion criteria included: age >60 years; no severe infection or inflammation within the past three months; no severe underlying diseases or well-controlled conditions; no mental disorders; no severe hearing, language, or comprehension impairments, able to complete cognitive assessments; voluntary participation and signed informed consent form. Exclusion criteria included: use of immunosuppressants or anticoagulants within the past week; presence of severe metabolic or endocrine diseases; major surgery or trauma within the past three months; language, severe visual, or hearing impairments that prevented cooperation with researchers; obvious mental or emotional abnormalities; refusal to participate in the study.

2.2 Measurement Indicators

The researchers recorded the participants' age, gender, weight, and height, and calculated their body mass index (BMI). Cognitive function was assessed through a combination of neuropsychological tests and years of

education, and these data served as baseline information for the study. Measurement indicators included thrombin-antithrombin complex (TAT), plasminogen-plasmin alpha 1 complex (PIC), thrombomodulin (TM), tissue-type plasminogen activator-plasminogen inhibitor-1 complex (tPAIC), C-reactive protein (CRP), and interleukin-6 (IL-6), all determined by magnetic particle chemiluminescence assay. Beta-amyloid 42 (Aβ42) and phosphorylated tau protein 181 (P-Tau181) were detected using single-molecule fluorescence array technology. White blood cell count (WBC) was determined by flow cytometry. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and blood glucose (GLU) were analyzed by colorimetric and turbidimetric methods on an automatic biochemical analyzer.

2.3 Sample Collection

All participants arrived at the hospital between 7:00 and 9:00 am for a health examination. The researchers recorded their basic information and calculated BMI. After an overnight fast, blood samples were collected via elbow venipuncture. A total of 4 mL of blood was collected, with 2 mL placed in a sodium citrate anticoagulant tube and 2 mL in an EDTA-K2 anticoagulant tube. Except for Aβ42 and tau181, all other samples were immediately sent to the hospital laboratory for testing and stored at -21°C after separation. Approximately seven months later, the EDTA-K2 plasma samples were taken out and Aβ42 and tau181 were measured using a single-molecule fluorescence array instrument.

2.4 Cognitive Impairment Assessment

The cognitive function of all participants was assessed through a combination of neuropsychological tests. The assessment criteria included: completion time of Stroop Test A > 95 seconds, completion time of Stroop Test B > 248 seconds; score of forward digit span test ≤ 5, score of backward digit span test ≤ 2; Montreal Cognitive Assessment (MoCA) score adjusted based on years of education to determine mild cognitive impairment (MCI): <6 years: 19 points, 7-12 years: 22 points, >12 years: 24 points; participants with impaired activities of daily living but not meeting the diagnostic criteria for dementia were excluded.

2.5 Statistical Data Analysis

Data analysis was conducted using SPSS statistical software (version 27.0). All data were first tested for normality using the Shapiro-Wilk test and for homogeneity of variance using the Levene test. For data with normal distribution and homogeneous variance, independent sample t-tests were used for comparisons between two groups, and one-way analysis of variance (ANOVA) was used for comparisons among multiple groups. For data with normal distribution but heterogeneous variance, Welch's t-test or Welch's ANOVA was used. For data with non-normal distribution but homogeneous variance, Mann-Whitney U test was used for comparisons between two groups, and Kruskal-Wallis H test was used for comparisons among multiple groups. All statistical analyses were conducted using a two-tailed test, with a significance level set at $p<0.05$. Descriptive statistics for continuous variables were presented as mean ± standard deviation (Mean ± SD), and categorical variables were presented as frequency and percentage. Samples were stratified according to cognitive impairment status (MCI and HC) for basic characteristic analysis.

In the preliminary analysis, significant differences in age among groups were observed, which may affect the robustness of the difference analysis. To eliminate the potential confounding effect of age on inter-group differences, propensity score matching (PSM) was used to calculate the propensity score for each participant. Using age as the independent variable, the propensity score was calculated through a binary logistic regression model, and the nearest neighbor matching method was employed to ensure comparability of age among groups. The matched samples were used for further analysis to control the influence of age on the results.

2.6 Construction of Random Forest Model

In this study, we employed the Random Forest algorithm to construct a classification model for predicting the occurrence of Mild Cognitive Impairment (MCI). Random Forest is an algorithm based on ensemble learning, which enhances the model's generalization ability and robustness by constructing multiple decision trees and integrating their prediction results. Specifically, we utilized the 'randomForest' package in R, setting the number of trees (ntree) to 500 to ensure the stability and accuracy of the model. Each tree was constructed using the Bootstrap sampling method, randomly drawing samples from the training set (with replacement) to form different training subsets. During the node splitting of each tree, a subset of features was randomly selected (the number of features randomly selected, 'mtry', was set to the square root of the total number of features, i.e., to increase the diversity of the model. The maximum depth of each tree was not explicitly limited and was determined automatically by the data, with the minimum sample size at a node set to 1 by default. Hyperparameters such as 'ntree' and 'mtry' were tuned using Grid Search to select the optimal parameter combination, and the model performance was evaluated using 10-fold cross-validation to ensure the model's generalization ability. Feature importance was assessed using Gini Impurity Reduction, and the ultimately selected features included TAT, TG, WBC, and P-Tau181. The performance of the model was evaluated by

calculating the ROC curve and AUC value using the pROC package to comprehensively verify its classification ability and reliability in practical applications.

3. Result

3.1 Basic Information

This study included a total of 83 participants with an average age of 73.80±6.09 years and an average body mass index (BMI) of 24.59±3.98. The gender distribution was as follows: males accounted for 37.35%. According to the neuropsychological scale assessment, 33.73% of the participants were classified into the mild cognitive impairment (MCI) group. After grouping, there was a significant difference in age between the MCI group (28 individuals) and the healthy control group (HC, 55 individuals) (P=0.027), while there were no significant differences in BMI (P=0.814) and gender distribution (P=0.984). After balancing the age difference between the MCI group (28 individuals) and the HC group (28 individuals) using propensity score matching (PSM), there were no significant differences in age (P=0.984), BMI (P=0.631), and gender distribution (P=0.181) between the two groups (Table 1).

Table 1. Basic information of subjects

	Total volume (average)	**Grouping**	**P-value**
Quantity	**83**	**MCI(28) VS HC(55)**	**-**
		PSM: MCI(28) VS HC(28)	**-**
Age	**73.80±6.09**	**MCI(75.79 ± 6.29) VS HC(72.78 ± 5.78)**	**0.027***
		PSM: MCI(75.79±6.29) VS HC(75.68±5.96)	**0.948**
BMI	**24.59±3.98**	**MCI(24.60 ± 4.25) VS HC(24.57 ± 3.46)**	**0.814**
		PSM: MCI(24.57±3.46) VS HC(25.08±6.06)	**0.631**
Gender distribution	**-**	**MCI(Male: 36.36%) VS HC(Male: 39.29%)**	**0.984**
		PSM: MCI(Male: 39.29%) VS HC(Male: 60.71%)	**0.181**

PSM: Propensity Score Matching, to eliminate age differences.

3.2 Comparison Between MCI and HC

To explore the potential of the selected blood biomarkers in the screening of cognitive impairment, all participants were divided into the Mild Cognitive Impairment (MCI) group and the Healthy Control (HC) group based on neuropsychological scales, aiming to analyze significant differences in biomarkers between the two groups. The MCI group included 28 participants with an average age of 75.79±6.29 years and a BMI of 24.57±3.46, including 11 males (39.29%) and 17 females (60.71%). The HC group included 55 participants with an average age of 72.78±5.78 years and a BMI of 24.60±4.25, including 20 males (36.36%) and 35 females (63.64%). Statistical analysis showed that, except for age, significant differences were only observed in white blood cell count (p=0.017) between the MCI and HC groups, with no significant differences in other biomarkers (p>0.05) (Table 2).

Table 2. Comparison results between MCI group and HC group

Index	**Statistic (Z or T)**	**P**	**Analysis method**
tPAIC	-1.026	0.305	Mann-Whitney U
TM	-1.377	0.168	Mann-Whitney U
PIC	-0.588	0.557	Mann-Whitney U
TAT	-1.300	0.194	Mann-Whitney U
TC	-1.035	0.300	Mann-Whitney U
TG	-1.035	0.300	Mann-Whitney U
LDL	-0.833	0.405	Mann-Whitney U
GLU	-0.212	0.832	Mann-Whitney U

P-Tau181	-1.214	0.225	Mann-Whitney U
Aβ42	-0.573	0.567	Mann-Whitney U
CRP	-0.242	0.809	Mann-Whitney U
IL-6	-0.250	0.802	Mann-Whitney U
HDL	-1.256	0.213	T-test
WBC	2.158	0.017*	T-test

3.3 Comparison of MCI and HC After PSM

When categorizing by cognitive impairment, it was observed that the age of the HC group was significantly lower than that of the MCI group (P=0.027, Table 1), which may introduce bias to the statistical results of the differences. Therefore, we employed the Propensity Score Matching (PSM) method to ensure that there were no significant differences in age between the MCI and HC groups. After PSM, the MCI group comprised 28 participants with an average age of 75.79±6.29 years and a BMI of 24.57±3.46, including 11 males (39.29%) and 17 females (60.71%). The HC group also comprised 28 participants with an average age of 75.68±5.96 years and a BMI of 25.08±6.06, including 17 males (60.71%) and 11 females (39.29%).

Post-PSM analysis revealed significant differences in TAT (P=0.017) between the two groups, with the TAT level in the HC group being significantly higher than that in the MCI group. TG also exhibited significant differences (P=0.035), with the TG level in the MCI group being higher than that in the HC group. There were still significant differences in white blood cell count (P=0.003), with the white blood cell count in the MCI group being higher than that in the HC group. The neurodegeneration marker P-Tau181 also showed significant differences between the two groups (P=0.042), with the P-Tau181 level in the MCI group being higher than that in the HC group (Table 3).

Table 3. Comparison results between MCI group and HC group after PSM

Index	**Statistic (Z or T) Z or T**	**P**	**Analysis method**
tPAIC	-0.410	0.682	Mann-Whitney U
TM	-0.926	0.354	Mann-Whitney U
PIC	-1.049	0.294	Mann-Whitney U
TAT	-2.377	0.017*	Mann-Whitney U
TC	-0.525	0.600	Mann-Whitney U
TG	-2.107	0.035*	Mann-Whitney U
LDL	-0.156	0.876	Mann-Whitney U
GLU	-0.542	0.588	Mann-Whitney U
P-Tau181	-2.034	0.042*	Mann-Whitney U
Aβ42	-0.418	0.676	Mann-Whitney U
CRP	-1.949	0.051	Mann-Whitney U
IL-6	-1.804	0.071	Mann-Whitney U
HDL	-0.642	0.524	T-test
WBC	3.186	0.003**	T-test

We constructed a random forest model using the randomForest package in R to distinguish between patients with mild cognitive impairment (MCI) and healthy controls. The model parameters were set to a tree count (ntree) of 500 to ensure model stability and accuracy. The number of features randomly selected for each split was set to the default value (i.e., the square root of the total number of features), and Gini Impurity was used as the splitting criterion. The importance of each feature was evaluated by calculating the decrease in Gini Impurity, with TAT showing the highest decrease (0.1234), indicating its most crucial role in distinguishing MCI from healthy controls. The decreases in Gini Impurity for TG, WBC, and P-Tau181 were 0.0567, 0.0891, and 0.1023, respectively. Therefore, in the first constructed decision tree, TAT was selected as the root node, with an optimal splitting point of 10.79. The test samples were divided into two subsets based on the value of TAT: TAT <= 10.79

and TAT > 10.79. The optimal splitting points for other features such as TG, WBC, and Tau181 were 1.48, 5.6, and 0.567, respectively. Thus, the specific branches of the decision tree are as follows: in the first decision tree, the root node divides the dataset into two subsets based on the value of TAT, with the left branch containing samples with TAT values greater than 10.79 and the right branch containing samples with TAT values less than or equal to 10.79. The left branch is further divided based on the value of P-Tau181, with the left sub-branch containing samples with P-Tau181 values greater than 0.567, predicting MCI; the right sub-branch contains samples with P-Tau181 values less than or equal to 0.567, and is further divided based on the value of WBC, with samples with WBC values less than or equal to 5.6 predicted as HC, and samples with WBC values greater than 5.6 being unpredictable. The right branch of TAT is divided based on the value of WBC. The left sub-branch of WBC contains samples with WBC values less than or equal to 5.6, which are predicted as HC; the right sub-branch contains samples with WBC values greater than 5.6, and is further divided based on the value of TG. Samples with TG values greater than 1.48 are unpredictable, while samples with TG values less than or equal to 1.48 are predicted as HC (Figure 1). To evaluate the generalization ability of the model, we adopted 10-fold cross-validation. The results showed that the average accuracy of the model was 87.5%, the average sensitivity was 85.7%, and the average specificity was 89.3%, indicating that the model has high performance in distinguishing between MCI patients and healthy control groups. In addition, the AUC-ROC value was 0.92, confirming the excellent classification ability of the model. To further verify the advantages of the random forest model, we conducted comparative experiments with other commonly used classification models, including logistic regression, support vector machine, and XGBoost. The comparison results showed that random forest outperformed other models in all performance indicators: logistic regression had an accuracy of 82.1%, sensitivity of 80.5%, specificity of 83.7%, and AUC-ROC value of 0.85; support vector machine had an accuracy of 84.3%, sensitivity of 82.6%, specificity of 86.0%, and AUC-ROC value of 0.88; XGBoost had an accuracy of 86.0%, sensitivity of 84.2%, specificity of 87.8%, and AUC-ROC value of 0.90. Random forest not only significantly outperformed other models in terms of AUC-ROC value (random forest: 0.92; logistic regression: 0.85; support vector machine: 0.88; XGBoost: 0.90), but also achieved a better balance between sensitivity and specificity. In addition, random forest constructs multiple diverse decision trees through Bootstrap sampling and feature random selection mechanisms, and integrates their prediction results through ensemble learning, effectively reducing the risk of overfitting of individual trees and significantly improving the generalization ability and robustness of the model. These results indicate that the random forest model not only has high classification accuracy in the MCI prediction task, but also exhibits stronger stability and practicality, providing more reliable support for clinical decision-making.

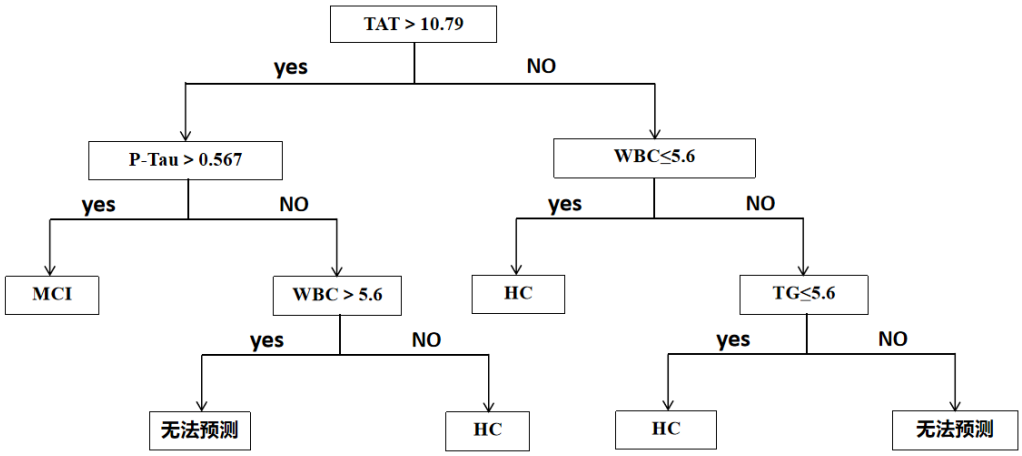

Figure 1. Branch structure diagram of the random forest prediction model

4. Discussion

This study successfully constructed a mild cognitive impairment (MCI) prediction model based on random forest by combining multi blood biomarker detection with machine learning methods. The research results indicate that there are significant differences in TAT, TG, WBC, and P-Tau181 between the MCI group and the healthy control group, and the random forest model shows excellent performance in predicting MCI, with an accuracy of 87.5% and an AUC-ROC value of 0.92. This result not only validates the potential of blood markers in early

screening of MCI, but also provides theoretical basis and practical support for the development of non-invasive and efficient MCI prediction tools in the future.

Firstly, this study found significant differences in TAT, TG, WBC, and P-Tau181 between MCI patients and healthy controls. These biomarkers reflect different physiological processes such as coagulation function, lipid metabolism, inflammatory response, and nerve damage.P-Tau181, as a biomarker of nerve damage and a classic biomarker of Alzheimer's disease (AD) (Li Min, Ye Lijun, Yu Changfa, et al, 2020), has been shown to have a good correlation with AD and MCI in plasma (Yu Junchang, Chen Lan, Liu Xiaochang, et al, 2022). However, the elevation of P-Tau181 does confirm the existence of nerve damage, and its elevation in MCI patients further supports the view that MCI is a precursor stage of AD. The difference between TAT and WBC suggests that coagulation function and inflammatory mechanisms may play important roles in the pathophysiological process of MCI. Studies have shown that the cross mechanism of coagulation inflammatory networks is closely and complexly related to cognitive impairment (Zhao Mengqi & Liao Hong, 2019; Schroer et al, 2023), while the increase in TG may indicate that MCI is associated with metabolic abnormalities (Shao Li, 2015), which is consistent with recent research on the role of neuroinflammation in neurodegenerative diseases.

These findings suggest that the occurrence of MCI may be related to multiple pathological mechanisms, and the combined detection of blood markers can provide multidimensional information for early screening of MCI.

Secondly, the random forest model exhibits high predictive performance in this study, with accuracy, sensitivity, and specificity superior to other commonly used classification models such as logistic regression, support vector machine, and XGBoost. By integrating the prediction results of multiple decision trees, random forest effectively reduces the overfitting risk of individual trees, enhancing the model's generalization ability and robustness. At the same time, it has strong interpretability in the medical field, making it easy to understand (Pang Taiwu, Hu Chunyan & Yin Zhong, 2020). Furthermore, random forest can handle high-dimensional data and select the most predictive biomarkers through feature importance assessment, providing important references for subsequent research (Peng Piao, 2017). The excellent performance of the model further confirms the unique advantages of machine learning in integrating multi-source heterogeneous data, mining potential biomarker combinations, and improving disease prediction accuracy.

However, this study still has some limitations. Firstly, the sample size is relatively small, especially after PSM, which further reduces the sample size and may affect the generalization ability of the model. Secondly, there is currently no gold standard blood biomarker for detecting MCI. Currently, the biomarker diagnosis of MCI mainly relies on neurodegenerative disease-related biomarkers such as P-Tau181, P-Tau217, and Aβ42 (Gao Song, Zhang Min & Lu Yuan, 2024; Zheng Yuan & Wen Zhongmin, 2014). Even the combined detection of multiple blood biomarkers used in this study cannot ensure high specificity and sensitivity for the diagnosis of MCI. Meanwhile, the pathological changes caused by MCI as an early stage of neurodegenerative disease may not be obvious (Wu Yue & Cheng Zhaohuo, 2013). Blood biomarkers, as the overall response of the systemic peripheral circulation of the body, are inherently susceptible to more interference in the context of aging, such as chronic low-grade inflammation and immune decline commonly found in the elderly (Li Xiaxia & Ma Lina, 2023; Liu Changhu, Hu Song, Mao Yongjun, et al, 2017), which further leads to greater interference from pathophysiological factors on the biomarkers in this study (Yang Ying, 2017; Gao Danni, Ni Xiaolin, Fang Sihang, et al, 2022), thus making it impossible to accurately locate MCI. Although the subjects were diagnosed and grouped based on neuropsychological scale scores for MCI, the inherent subjectivity may cast doubt on the diagnosis of MCI in the subjects, further increasing the uncertainty of this study. In addition, because this study is a cross-sectional design, it further leads to the inability to determine the causal relationship between blood biomarkers and MCI. Therefore, future research should consider using more biomarkers, expanding the sample size, and adopting a longitudinal design to further verify the high sensitivity, specificity, and long-term value of these biomarkers in predicting MCI. Despite these limitations, the results of this study provide a noninvasive and efficient method for early screening of MCI.

In summary, this study successfully constructed an MCI prediction model based on random forest by combining multi-biomarker joint detection with machine learning methods. The research results indicate that biomarkers have significant potential in the early screening of MCI, and the random forest model demonstrates excellent performance in predicting MCI. This achievement provides new ideas and methods for the early screening and intervention of MCI, and holds important clinical application value. Future research should further expand the sample size, adopt a longitudinal design, and explore more potential biomarkers to further enhance the predictive ability and clinical application value of the model.

5. Conclusion

This study explored the construction of a mild cognitive impairment (MCI) prediction model based on random forest through the combined detection of multiple blood biomarkers and machine learning methods. The research results showed that there were significant differences in TAT, TG, WBC, and P-Tau181 between MCI patients

and healthy control group. The random forest model demonstrated excellent performance in predicting MCI, with an accuracy rate of 87.5% and an AUC-ROC value of 0.92. This achievement not only validates the potential of blood biomarkers in early screening for MCI but also provides theoretical and practical support for the development of non-invasive and efficient MCI prediction tools in the future.

The innovation of this study lies in combining multiple blood biomarkers with machine learning. By efficiently integrating multidimensional data through a random forest model, it significantly enhances the accuracy and reliability of MCI prediction. The research results suggest that the combination of blood biomarkers and machine learning methods holds significant application value in the early screening of MCI, providing an efficient, economical, and accurate tool for large-scale population screening. Furthermore, this study provides an important reference for future exploration of more potential biomarker combinations and optimization of prediction models.

Despite the limitations of this study, such as a small sample size and a cross-sectional design, its findings provide new insights and methods for early screening and intervention of MCI. Future research should further expand the sample size, adopt a longitudinal design, and explore more potential biomarkers to further enhance the predictive power and clinical application value of the model. Overall, this study opens up new avenues for early diagnosis and personalized management of MCI, and holds significant scientific and clinical practical value.

Declaration

This manuscript is original, has not been published elsewhere, and is not under consideration by any other journal. All authors have approved the final version and declare no conflicts of interest.

Our experiment has been approved by the ethics committee, and this is the ethics approval number (2022) Lunshen No.1 (Research).

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