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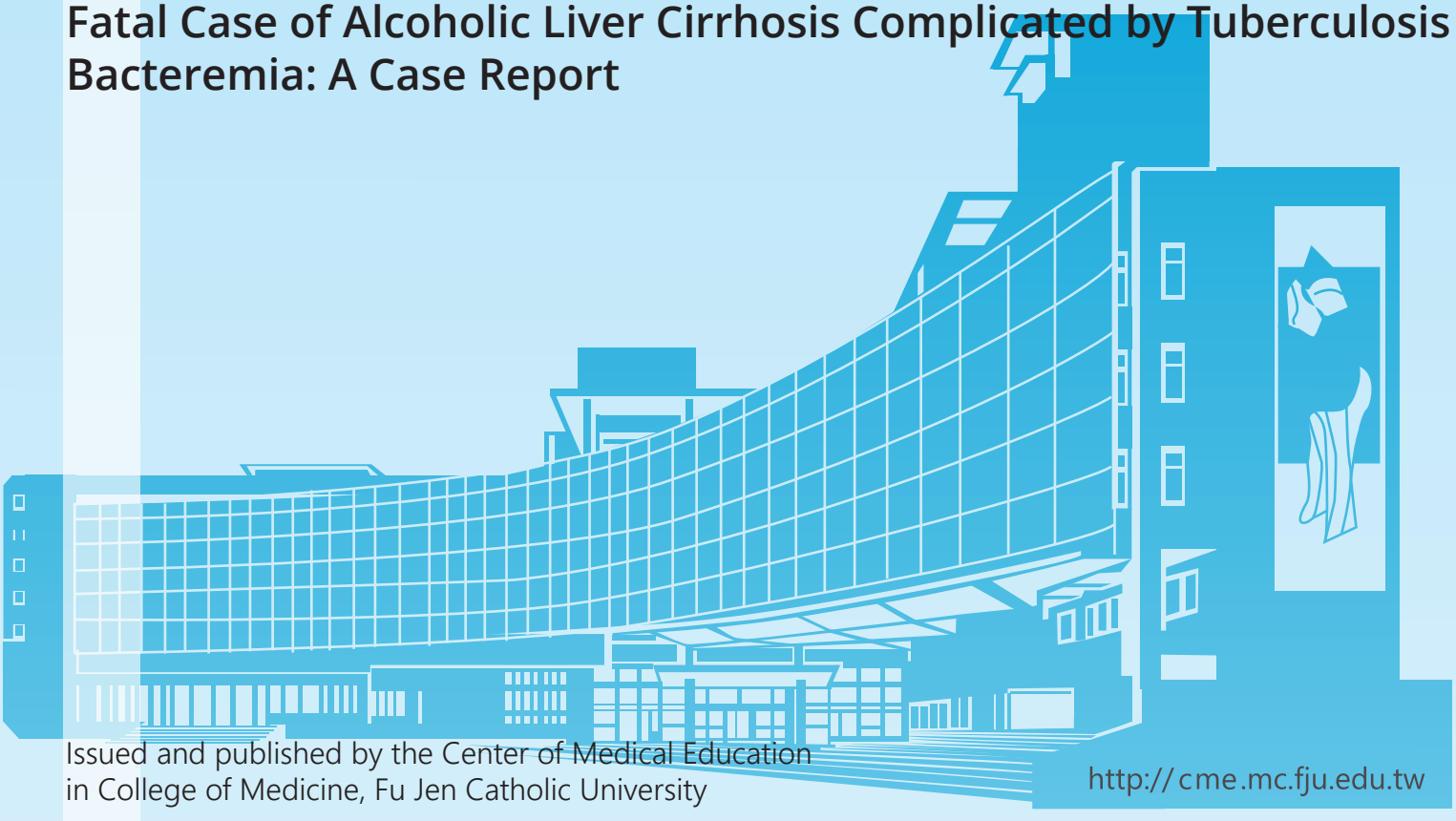

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Original Research Article

Establishing standardized murine models of intestial cystitis: comparative insights from lipopoly saccaride, acetic acid, and cyclophosphamide exposure

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ABSTRACT

Background: Interstitial cystitis (IC) is a chronic bladder disorder characterized by pelvic pain, urinary urgency, and frequent occurrence without infection. Animal models using chemical inducers are essential for studying IC pathophysiology; however, standardized comparative evaluations are scarce. ***Methods:*** This study compared three chemical-induced IC models: lipopolysaccharide (LPS), acetic acid (AA), and cyclophosphamide (CYP), in female C57BL/6 mice (n = 32, 8/group). Cystometric parameters including basal pressure, threshold pressure, peak pressure, intercontraction interval (ICI), and non-voiding contractions (NVCs) were measured. Bladder histology was assessed using hematoxylin and eosin staining. The expression of caspase-9, NF-κB, and cytokeratin-20 (CK20) was analyzed using western blotting. ***Results:*** AA-treated mice exhibited the most severe urothelial disruption, with significantly elevated caspase-9 (3.1-fold) and NF-κB (2.8-fold) expression as well as reduced CK20 levels ($p < 0.05$). Functionally, the AA group showed a shortened ICI (82.4 ± 10.1 s) and increased NVCs. LPS induced prolonged ICI (161.3 ± 8.9 s) with

moderate inflammation, while CYP increased basal pressure (14.7 ± 1.6 cmH_2O) and NVCs, indicating detrusor overactivity. ***Conclusion:*** Among the tested models, acetic acid induction yielded the most consistent inflammatory, histological, and functional IC phenotypes, making it a robust model to study epithelial injury and acute bladder inflammation. These findings provide a standardized framework for selecting appropriate IC models for translational research.

Keywords: interstitial cystitis, mouse model, cystometry, inflammation, acetic acid, NF-κB

INTRODUCTION

Interstitial cystitis (IC), also referred to as bladder pain syndrome (BPS), is a chronic, non-infectious disorder of the lower urinary tract characterized by persistent bladder wall inflammation in the absence of an identifiable infection. Clinically, it presents with chronic pelvic pain, urinary urgency, increased frequency, and suprapubic discomfort, all of which contribute to a substantial reduction in quality of life, particularly among women and elderly individuals[1] Although the exact pathogenesis of IC remains elusive, several mechanisms have been proposed, including urothelial dysfunction, immune dysregulation, neurogenic inflammation, and epithelial barrier disruption. Despite ongoing investigations, the inflammatory pathways and molecular events underlying bladder tissue injury and symptom manifestation in IC have not been fully elucidated[2]. This gap in our understanding is primarily because of the absence of robust and translatable animal models that can accurately reproduce the chronic, heterogeneous, and multifactorial characteristics of human IC.

Research indicates that IC is common, potentially affecting up to one in five women, with a female-to-male ratio of about 10:1. Its prevalence is hard to define due to frequent misdiagnosis with other pelvic pain conditions. Stress is often considered a factor, but supporting evidence is limited. Possible causes under study include allergies, infections, nervous system disorders, and urinary toxins, though the exact origin remains unclear[3]. Therefore, the development of reliable, reproducible, and mechanistically informative animal models is essential to deepen our understanding of cystitis pathogenesis and to facilitate the preclinical assessment of novel therapeutic interventions. Establishing standardized and reproducible animal models is essential to facilitate translational progress in IC research. Among the available methods, chemical inducers such as lipopolysaccharide (LPS), acetic acid (AA), and cyclophosphamide (CYP) are frequently employed to mimic various pathological features of IC. The following section presents a direct comparative assessment of the three models under harmonized experimental conditions.

Animal models, particularly murine models, have been extensively used to mirror the pathophysiological characteristics of human bladder inflammation. Chemical inducers such as LPS, AA, and CYP are routinely used because they elicit overlapping yet distinct inflammatory pathways[4]. LPS, a component of gram-negative bacterial membranes, activates Toll-like receptor 4 (TLR4), triggering pro-inflammatory signaling that disrupts the urothelial barrier and recruits immune cells to the bladder wall[5]. AA provokes cystitis by directly irritating the urothelium, thereby modeling non-infectious bladder inflammation and enabling studies on nociception and urinary urgency[6]. CYP, a chemotherapeutic prodrug, is metabolized to acrolein, which induces severe urothelial toxicity characterized by edema, hemorrhage, and robust inflammatory cell infiltration, thus serving as a model of hemorrhagic cystitis[7]. Together, these chemically induced models offer complementary insights into the diverse mechanisms that drive bladder pathology.

Although LPS-, AA-, and CYP-induced cystitis models have been individually characterized in previous studies, variations in dosing regimens, evaluation time points, and outcome measures have limited the efforts toward direct comparison and experimental standardization. Furthermore, only a limited number of studies have simultaneously evaluated the functional, histological, and molecular parameters across these models, thereby restricting their comparative value and translational applicability in preclinical bladder inflammation research. Recent studies have highlighted the necessity of thorough evaluation of experimental models of cystitis, emphasizing not only urodynamic (functional)

alterations but also detailed histopathological assessment and molecular profiling[8]. Critical molecular markers include the expression levels of proinflammatory cytokines, chemokines, and proteins associated with tissue remodeling and epithelial repair, all of which provide valuable insights into the extent and progression of bladder inflammation[9]. Although LPS, AA, and CYP are commonly used as chemical agents to induce cystitis, comparative analyses of these models under uniform and standardized experimental protocols remain limited[10]. Such comparative characterization is essential to guide the selection of appropriate models aligned with specific research aims and to enhance the translational relevance of preclinical findings. Accordingly, the present study aimed to develop a standardized murine model of acute cystitis using LPS, AA, and CYP, and to comprehensively evaluate the associated changes in bladder function, histological integrity, and molecular responses to facilitate future therapeutic investigations.

MATERIALS AND METHODS

1.1 Study layout

To reduce variability in IC induction and enhance translational consistency, we implemented a standardized protocol to compare the pathological and functional outcomes of three chemically induced murine models: LPS, AA, and CYP. Adult female C57BL/6 mice were randomly assigned to four groups (n = 8 per group): normal control (NC), LPS, AA, and CYP. The LPS and AA groups were administered the respective agents via transurethral instillation, while the CYP group received intraperitoneal administration. The NC group received normal saline via the corresponding route and served as a procedural control (Figure 1). Subsequent analyses included cystometric assessment (CMG) of bladder function, histological evaluation of bladder tissue, and western blot analysis of inflammation-related molecular markers.

1.2 Experimental animals

Adult female C57BL/6 (B6) mice, 8 weeks of age at the time of procurement (Jackson Laboratory, Bar Harbor, ME, USA), were used in this study. All experimental procedures were conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki and were approved by the Institutional Animal Care and Use Committee (IACUC) of Fu Jen Catholic University (Approval No.: A11082 from: 2022-08-01 to 2025-07-31). The animals were housed under controlled conditions in standard polypropylene cages at 25 ± 1 °C with a 12-hour light/dark cycle. All mice had free access to sterile food and water, and were maintained under aseptic conditions throughout the experimental period.

1.3 Pathophysiological induction of interstitial cystitis via LPS, AA, and CYP Exposure

Surgical intervention was performed in preparation for IC model induction to enable the subsequent evaluation of bladder changes. The surgical procedure for catheter implantation and subsequent cystometric evaluation were based on our previous methodology (1). Briefly, mice were anesthetized via intraperitoneal injection of Zoletil 50 (tiletamine/zolazepam, 25 mg/kg) combined with xylazine (7.5 mg/kg). A midline abdominal incision is made to expose the bladder. A small opening was created at the dome of the bladder and one end of a polyethylene-50 catheter (Natsume Seisakusho Co., Tokyo, Japan) was inserted into the bladder lumen. The bladder was sutured to ensure watertight sealing. The external end of the catheter was tunneled subcutaneously through the left flank and exteriorized in the posterior cervical region. Proper catheter function was confirmed by verifying the unobstructed urine flow without leakage at the bladder incision site. The catheter was secured and the abdominal wound was closed. To prevent postoperative infection, cefprozil (15 mg/kg) was administered intramuscularly and the mice were monitored in a warmed recovery chamber until full recovery from anesthesia.

To establish the IC model, a total of 32 female C57BL/6 (B6) mice aged 8 weeks were used. Twenty-four mice were randomly assigned to receive one of three cystitis-inducing agents, LPS, AA, or CYP, whereas the remaining eight mice underwent a sham procedure and served as the NC group. Three days post-surgery, the experimental groups underwent chemical induction of IC. The LPS group received a single transurethral instillation consisting of protamine sulfate (100 μL, 10 mg/mL) followed by a 5-minute dwell time, then normal saline (100 μL), and finally LPS derived from Escherichia coli (100 μL, 500 μg/mL) with another 5-minute dwell time (Sigma-Aldrich, St. Louis, MO, USA). The AA group received 1% acetic acid (100 μL) transurethrally for 1 min and was administered once daily over three non-consecutive days. The CYP group was treated with intraperitoneal injections of cyclophosphamide at a dose of 70 mg/kg body weight, once daily for three consecutive days (Sigma-Aldrich, St. Louis, MO, USA). The animals were monitored daily for signs of pain or distress, including abnormal

behavior, reduced mobility, and hunched posture.

2. 4 Quantitative cystometry (CMG) and functional characterization of bladder activity

Subsequently, all animals underwent CMG evaluation. Each mouse was gently placed on the experimental platform and the external end of the previously implanted PE-50 catheter was connected to a pressure transducer system. Continuous cystometric recordings were initiated using the MP3 pressure transducer in conjunction with Biopac Student Lab 4.1 software (Biopac Systems Inc., Santa Barbara, CA, USA). The following CMG parameters were recorded and analyzed: basal pressure, peak voiding pressure, threshold pressure, voided volume (VV), non-voiding contractions (NVC), and inter-contraction interval (ICI), providing a comprehensive assessment of bladder function.

2.5 Hematoxylin and Eosin (H&E)–Based Histological Assessment

Following the completion of CMG recordings, the mice were euthanized via intraperitoneal administration of a high dose of pentobarbital sodium. The bladders were carefully excised and immediately fixed in 10% neutral buffered formalin (w/v) for 24 h to ensure optimal tissue preservation. Four animals from each experimental group were randomly selected for the histological analysis. The bladders were bisected and processed using standard histological procedures, including dehydration using a graded ethanol series, post-fixation, and paraffin embedding.

For paraffin embedding, tissue specimens were placed in stainless-steel molds on a heated plate maintained at 50–60 °C. Molten paraffin wax was poured to fully embed the specimens, which were then allowed to solidify at RT. Excess wax was trimmed and paraffin blocks were sectioned into 3 μm-thick slices using a microtome. Sections were mounted on positively charged glass slides, dewaxed with xylene, and rehydrated using a descending ethanol series (100, 95, 90, 80, and 70%), followed by immersion in double-distilled water (ddH_2O) for 5 min. The prepared tissue sections were stained with hematoxylin and eosin for general morphological assessment. Staining was performed according to the protocols described in our previous study[1] with minor modifications.

2.6 Bladder Protein Extraction and Western Blotting

Five mice per group were allocated for molecular analysis and their bladder tissues were processed for immunohistochemical staining and western blot evaluation. The protocol for protein extraction and immunoblotting was adapted from Wang et al. (2017)[11], with minor modifications. Bladder tissues were homogenized in 300 μL of T-PER™ tissue protein extraction reagent (78510; Thermo Fisher Scientific, Waltham, MA, USA) supplemented with protease inhibitors (04693132001; Roche, Basel, Switzerland) at a volume ratio of 25:1 (v/v) using an MP FastPrep-24 5G homogenizer (MP Biomedicals, Santa Ana, CA, USA). Following centrifugation at 12,000 rpm for 15 min at 4 °C, the supernatants were collected and the total protein concentration was determined using the BCA Protein Assay Kit (5000006; Bio-Rad, Berkeley, CA, USA).

Equal amounts of protein (20 μg per lane) were denatured, resolved on 10% or 15% SDS-PAGE gels, and transferred onto polyvinylidene fluoride (PVDF) membranes (1620177; Bio-Rad, USA). Membranes were blocked in PBST buffer containing 5% non-fat dry milk at room temperature for 1 hour and incubated overnight at 4 °C with primary antibodies diluted in 5% milk: anti-cytokeratin 20 (SC271183; Santa Cruz Biotechnology, USA; 1:1000), anti-caspase-9 (ab202068; Abcam, UK; 1:2000), anti-NF-κB p65 (10745-1-AP; Proteintech, USA; 1:1500), anti-GAPDH (60004-1-Ig; Proteintech, USA; 1:20,000), and anti-β-actin (SC47778; Santa Cruz Biotechnology, USA; 1:5000). After washing, the membranes were incubated for 1 h at room temperature with the appropriate HRP-conjugated secondary antibodies: anti-rabbit HRP (115-035-003; Jackson ImmunoResearch, USA; 1:15,000 for caspase-9 and NF-κB p65) and anti-mouse HRP (Jackson ImmunoResearch; 1:15,000 for GAPDH and 1:20,000 for β-actin). Immunoreactive bands were visualized using immunoblot western chemiluminescent HRP substrate (WBKLS0500; Merck, Rahway, NJ, USA), and images were captured using the VisionWorks® system (Analytik Jena, Jena, Germany). Band intensities were quantified using Image Lab software (version 3.0; Bio-Rad, USA) and relative protein expression was compared across groups. All Western blot experiments were independently performed in duplicate to ensure data reliability and reproducibility.

2.7 Statistical Analysis

All data are presented as mean ± standard deviation (SD). Statistical comparisons among groups were performed using the Student's t-test. Statistical significance was set at $P < 0.05$. All

analyses were conducted using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). A total of 32 animals were allocated to the study, with eight mice per group across the four groups. Power analysis and sample size estimation were performed using SPSS v18.0. For CMG and bladder functional analyses, the use of eight animals per group (n = 32) provided a statistical power of 98% at an alpha level of 0.05. For histological and western blot analyses, 4 animals per group (n = 16) were included, achieving a statistical power of 82% with the same significance threshold.

RESULTS

3.1 Comparative evaluation of bladder function in chemically induced IC models

CMG analysis revealed distinct alterations in voiding parameters among the chemically induced IC models compared to the NC group (Figure 2A). Among the three experimental groups, AA-treated mice exhibited the most prominent features of bladder overactivity, characterized by a significant increase in peak voiding pressure and higher frequency of non-voiding contractions (NVCs). These findings indicate detrusor hyperactivity and reduced voiding efficiency, which closely mirror the functional abnormalities commonly observed in patients with IC/BPS. Quantitative analysis of CMG parameters (Figure 2B) demonstrated that AA significantly increased peak pressure compared to the NC group ($p < 0.05$), while also inducing a notable increase in NVC frequency. Although ICI was more prolonged in the LPS group, AA-treated animals maintained a relatively elevated ICI, along with increased VV and enhanced pressure dynamics, indicating a more complex voiding phenotype involving both urgency and storage dysfunction. Collectively, these findings suggest that AA induces a robust and clinically relevant model of IC that combines significant functional impairment with marked tissue pathology. Therefore, the AA model may offer superior translational value for studying the pathophysiology of IC and evaluating potential therapeutic interventions.

3.2 Histological evaluation of bladder architecture in chemically induced IC models

Representative histological images of bladder tissues stained with hematoxylin and eosin (H&E) are presented in Figure 3A, comparing the morphological alterations across the control and IC-induced groups. AA-treated bladders exhibit marked pathological remodeling characterized by pronounced urothelial thickening, submucosal expansion, and muscularis hypertrophy accompanied by substantial inflammatory cell infiltration. These features closely resemble the structural hallmarks of chronic IC/BPS, indicating a sustained epithelial injury and compensatory muscular adaptation. In contrast, bladders from the LPS group showed moderate epithelial irregularity with localized stromal edema and less inflammatory infiltration, suggesting a subacute inflammatory phenotype. The CYP group demonstrated relatively preserved mucosal integrity with localized disruptions and mild thickening of the urothelium and detrusor, indicating limited yet detectable histological compromise. Tissues from the control group maintained a well-organized architecture with a thin urothelium, intact transitional epithelium, and compact detrusor muscle devoid of pathological changes.

The quantitative morphometric analysis (Figure 3B) further corroborated these observations. Urothelial thickness was significantly increased in the AA group, exceeding that observed in CYP, LPS, and control tissues, consistent with epithelial hyperplasia and barrier dysfunction. Similarly, detrusor muscle thickness was markedly elevated in the AA group, reflecting hypertrophic adaptation to chronic inflammatory stress. LPS-treated bladders showed a trend toward muscle thinning, whereas the CYP and control groups retained relatively stable smooth muscle profiles. Collectively, these findings underscore the superior translational validity of the AA-induced model, as it recapitulates both epithelial and smooth muscle pathologies characteristic of human IC/BPS, thereby providing a more robust and clinically relevant platform for mechanistic investigations and therapeutic evaluation.

3.3 Comparative evaluation of protein expression in ic mouse models induced by CYP, LPS, and AA

Western blot analysis was used to evaluate the expression of key proteins associated with epithelial differentiation, inflammation, and bladder structural integrity across the experimental groups. As shown in Figure 4A, Keratin 20 (CK20) expression, a marker of urothelial maturation and epithelial remodeling, exhibited significant inter-group variation. The AA group showed a marked upregulation of CK20, with expression levels significantly higher than those observed in the control, CYP, and LPS groups ($p < 0.01$). In contrast, the CYP and LPS groups showed relatively low and comparable expression, which did not differ significantly from the

control group. This differential expression pattern suggests that AA-induced injury elicits a strong epithelial remodeling response, whereas the CYP and LPS models result in minimal to moderate impact on urothelial differentiation.

Further investigation of apoptotic and inflammatory mediators (Figure 4B) revealed notable differences between models. Caspase-9 expression, a key initiator of intrinsic apoptosis, was significantly upregulated in the CYP group compared to the control group ($p < 0.05$), followed by moderate elevations in the LPS and AA groups. Similarly, cleaved caspase-9, which is indicative of active apoptotic signaling, was prominently expressed in the CYP group, with significantly lower levels observed in both the LPS and AA groups ($P < 0.05$), suggesting that CYP-induced cystitis was more extensive. Notably, NF-κB expression, a pivotal transcription factor that regulates inflammatory responses, was significantly elevated in all three IC models relative to that in the controls ($p < 0.01$). The LPS and AA groups exhibited the highest NF-κB levels, with the AA group trending slightly higher, although the difference between the AA and LPS groups did not reach statistical significance. These results highlight the robust inflammatory activation in both models, with AA demonstrating a greater degree of epithelial remodeling and inflammation than CYP or LPS.

DISCUSSION

Understanding the complex mechanisms underlying IC remains a major scientific hurdle, limiting the advancement of effective treatment options. This complexity has also hampered the development of reliable animal models that closely reflect the clinical features of patients. Given the growing emphasis on aligning experimental research with clinical reality, there is a pressing need to design translational models that faithfully replicate the chronic multifaceted pathology of IC in humans. In the present study, we systematically compared three commonly used chemically induced models, LPS, AA, and CYP, to evaluate their effectiveness in mimicking IC/BPS pathophysiology. Comprehensive urodynamic assessments, histological evaluations, and molecular analyses were performed to identify representative and reproducible models. Establishing a reliable animal model of IC requires a comprehensive understanding of its complex pathophysiology. Although the precise etiology of IC remains unclear, several mechanisms have been implicated, including increased mast cell infiltration within the bladder wall, disruption of the protective glycosaminoglycan (GAG) layer of the urothelium, and autoimmune dysregulation. Various rodent models have been developed based on these pathogenic frameworks to replicate the clinical and molecular features of IC in humans[12]. For instance, the AA-induced model elicits altered expression of key urothelial markers such as uroplakin III (UPK3) and zonula occludens-1 (ZO-1), which are also consistently observed in human IC specimens[13]. CYP exposure is associated with elevated expression of pro-inflammatory cytokines and increased mast cell density within the bladder tissue, yet typically without causing overt hemorrhage or widespread epithelial damage[14]. Furthermore, both systemic administration and intravesical instillation of LPS have been shown to provoke robust inflammatory responses characterized by mast cell activation, cytokine release, and leukocyte infiltration at the bladder mucosal interface, hallmarks that mirror the immunopathological landscape of IC in humans[15]. Preclinical models offer valuable platforms for elucidating disease mechanisms and for evaluating potential therapeutic interventions.

CMG evaluation remains a cornerstone for the functional characterization of bladder pathophysiology in experimental IC/BPS models.[16]. In the current study, distinct cystometric signatures were observed across CYP-, LPS-, and AA-induced models in comparison with controls, highlighting variations in bladder dysfunction patterns linked to each irritant. The CYP-induced IC model presented significantly elevated basal and threshold bladder pressures along with marked reductions in VV and ICI, indicating a hyperactive bladder state. These findings align with clinical observations of increased urgency and frequency in acute IC/BPS, where bladder capacity is compromised due to inflammation-driven afferent sensitization. Previous studies have demonstrated that CYP causes urothelial barrier disruption, mast cell activation, and neurogenic inflammation, all of which contribute to detrusor overactivity and NVCs[17]. This was reflected in our data, in which the CYP group exhibited the most pronounced NVCs among the experimental models, suggesting an enhanced afferent excitability and compromised voiding coordination.

In contrast, the AA model demonstrated intermediate elevations in basal and threshold pressures, and a moderate reduction in VV, whereas its ICI remained comparable to that of NC. Previous research supports that AA induces robust neurogenic inflammation through direct chemical irritation, leading to transient epithelial disruption and release of inflammatory media-

tors[16]. Notably, the relatively stable ICI and partially retained voiding function despite severe histological damage indicated a dichotomy between structural injury and bladder reflex activity in the AA model, possibly reflecting early compensatory mechanisms before detrusor decompensation. Overall, each model reflects distinct pathophysiological features of IC: CYP mimics acute inflammation with functional impairment; LPS reflects chronic inflammation with preserved function; and AA exhibits early epithelial damage with functional compensation. Among these, the AA model has emerged as a balanced platform, showing both significant histological injury and moderate urodynamic changes, making it a valuable tool for evaluating therapeutic agents targeting urothelial integrity and inflammatory resolution.

To further elucidate the structural underpinnings of the functional alterations observed in cystometric recordings, we conducted histological analyses of bladder tissue architecture across the experimental groups. Although urodynamic parameters such as basal pressure, ICI, and VV reflect real-time detrusor activity and afferent signaling dynamics, histological assessments offer insights into the morphological integrity of the urothelium and detrusor muscle layers. This integrative approach enables a more comprehensive understanding of the relationship between inflammation-induced structural remodeling and corresponding bladder dysfunction in distinct IC/BPS models.

H&E staining revealed notable histomorphological differences across the experimental groups, reflecting distinct degrees of bladder injury and structural remodeling. In the control group, the urothelium appeared intact, with a clearly demarcated umbrella cell layer and a well-organized lamina propria. The detrusor muscle bundles were compact and uniformly distributed. In the CYP-treated group, mild urothelial thickening was observed along with occasional epithelial sloughing and submucosal edema. Quantitatively, CYP induced a moderate increase in urothelial thickness (~44 μm vs. 39 μm in the control group), consistent with early epithelial injury and inflammatory infiltration. The detrusor muscle layer showed slight thinning compared to the control, potentially due to inflammation-induced smooth muscle disruption or localized fibrosis, which aligns with previous findings linking CYP-induced IC with neuroinflammation and urothelial denudation (Birder et al., 2018)[18]. The LPS-treated group exhibited more pronounced epithelial hyperplasia with basal layer disorganization and mild leukocyte infiltration. The urothelium showed irregular thickness (~42 μm) and the detrusor muscle appeared relatively atrophic (~520 μm), suggesting impaired structural integrity. These findings support the notion that LPS induces chronic inflammation via TLR4-mediated pathways, leading to mucosal remodeling and detrusor decompensation[19].

Notably, AA exhibited the most extensive histological abnormalities. The urothelium was markedly thickened (~50 μm) and irregular with extensive epithelial exfoliation and pronounced subepithelial edema. Despite severe urothelial damage, detrusor muscle thickness remained relatively preserved (~670 μm), indicating that AA induced a more superficial injury that spared the muscle layers in the early phases. This aligns with prior evidence that AA triggers acute neurogenic inflammation and mucosal barrier breakdown without immediately compromising the deeper muscle architecture[16]. These structural changes collectively reflect the varying pathophysiological effects of the different IC/BPS inducers. While CYP and LPS models primarily induce inflammatory and immune responses that affect both epithelial and muscular compartments, AA appears to target the urothelium more aggressively. Interestingly, despite severe epithelial disruption in AA, detrusor integrity remained relatively intact, which could explain the intermediate urodynamic outcomes observed in this model. This distinction is critical for selecting appropriate models for mechanistic studies and therapeutic evaluation of IC/BPS. The protein expression profiles of α-SMA and CK20, two critical markers of bladder structural integrity and urothelial differentiation, were evaluated to assess pathological remodeling in various IC/BPS animal models. GAPDH was used as a loading control for normalization. The expression levels of α-SMA, a cytoskeletal protein indicative of the smooth muscle contractile phenotype and fibrosis, remained relatively consistent across the groups, with a slight increase noted in the LPS and AA models compared to the control. Although not statistically significant, this suggests a trend of mild detrusor hypertrophy or fibroblast-to-myofibroblast transition, particularly in chemically induced inflammatory settings. This observation aligns with previous reports linking chronic bladder inflammation to smooth muscle remodeling and hypercontractility[20;21].

In contrast, CK20 is a terminal differentiation marker of umbrella cells in the urothelium,[22] and exhibited a striking upregulation in the AA-treated group relative to all other groups,

including the control group. This significant elevation ($p < 0.01$) underscores the profound alterations in urothelial phenotype and barrier function following AA exposure. These findings are consistent with histological observations of extensive urothelial damage and regeneration in the AA model, reflecting active epithelial remodeling and compensatory differentiation. In support of this, CK20 overexpression has previously been reported in patients with chronic cystitis and epithelial injury[23;24].

Conversely, both CYP and LPS groups showed markedly reduced CK20 expression, indicating a potential suppression or delay in urothelial regeneration, possibly due to ongoing inflammation or epithelial denudation[25]. These results suggest that, while AA induces more severe and acute epithelial damage, it may concurrently stimulate a regenerative response, whereas CYP and LPS models reflect more persistent epithelial dysfunction without effective restitution. Collectively, these findings reinforce the notion that different IC/BPS models can recapitulate the distinct facets of the disease spectrum. AA-induced injury appears to provoke robust epithelial turnover and repair, as evidenced by elevated CK20 levels, whereas the LPS and CYP models manifest sustained epithelial stress without substantial regenerative activity. Understanding these model-specific responses provides critical insights for selecting appropriate platforms for therapeutic intervention and mechanistic studies in urothelial pathobiology.

STUDY NOVELTY AND CONSIDERATIONS

This study offers a standardized, multi-parametric evaluation of three chemical-induced mouse models of IC, LPS, AA, and CYP, to assess urodynamic function, histological damage, and molecular markers. Unlike previously isolated evaluations, this comparative approach enhances the translational relevance. Among these models, AA-induced IC exhibited the most pronounced urothelial disruption, inflammatory infiltration, and elevated expression of caspase-9 and NF-κB, highlighting its suitability for studying inflammation-driven bladder pathologies. Although this study establishes a robust comparative framework for IC models, it has certain limitations. The short-term assessment captures acute rather than chronic responses, and the use of only female mice limits the sex-based generalizability. Behavioral measures of pain and urgency were not included and broader molecular profiling was not performed. Nonetheless, this study offers a valuable foundation for standardized IC model evaluations in preclinical research.

CONCLUSIONS

This study provides a systematic and side-by-side evaluation of three chemically induced IC mouse models under a unified experimental framework. The AA model exhibited the most pronounced epithelial disruption and inflammatory marker expression, thus positioning it as a robust model for studying acute IC pathology. The LPS and CYP models demonstrate features reflective of chronic and neurogenic inflammation, respectively. These findings emphasize the importance of model selection based on targeted research goals. While limited to acute-phase assessment, female-only subjects, and a focused biomarker panel, future studies should address these limitations by incorporating chronic time points, sex-based comparisons, behavioral endpoints, and broader molecular profiling. Thus, this work not only establishes a standardized benchmark for IC modeling but also lays the groundwork for future refinement and translational advancement.

Data availability statement:

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. Owing to ethical considerations and confidentiality obligations, the data are not publicly accessible; however, they will be provided to qualified researchers in full compliance with institutional and regulatory guidelines governing data sharing.

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Consent and Ethical Statement:

This study was conducted without the involvement of human participants. All animal-related experiments were performed under strict ethical standards, aligning with the Declaration of Helsinki and internationally endorsed animal welfare frameworks. The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Fu Jen Catholic University (Approval No.: A11082), with authorization valid from August 1, 2022, through July 31, 2025. Every procedural step reflects an

unwavering commitment to humane treatment, scientific integrity, and institutional accountability. Furthermore, the study adhered to the 3Rs principles—Replacement, Reduction, and Refinement—to ensure that ethical considerations remained integral to the research process.

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Conflict of Interest:

The authors declare no commercial or financial conflicts of interest that could be construed as potential biases influencing the conduct, analysis, or reporting of this study.

Author Contributions:

Hung-Chune Maa: Funding Acquisition, Supervision,Wen-Chun Hsu : Funding Acquisition, Methodology, Investigation, Data Curation, Formal Analysis.Chao-Yuan Chang: Resources, Validation, Funding Acquisition. Chellappan Praveen Rajneesh: Writing—Original Draft, Review & Editing, Visualization, Data Interpretation. Huang jing yong: Validation, Visualization, Methodology, Investigation. Yi No-Wu: Conceptualization, Project Administration, Review & Editing, Technical Support.

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FIGURE AND FIGURE LEGENDS

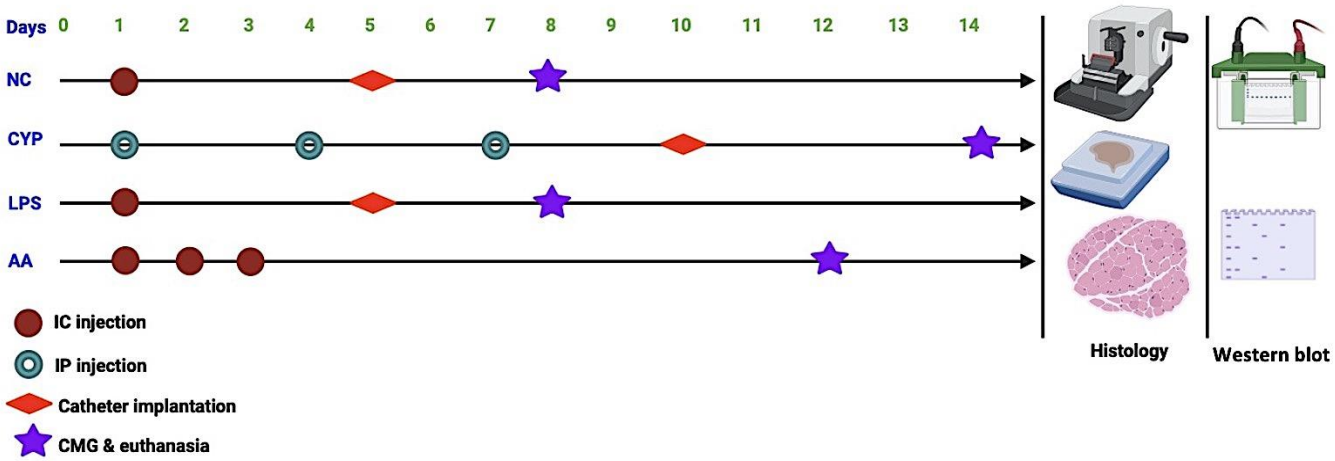

Figure 1. Experimental timeline for IC model induction and outcome assessments

Experimental timeline for the induction of IC model in mice using LPS, AA, and CYP. Red circles indicate IC injections, blue circles represent intraperitoneal (IP) injections, red diamonds denote catheter implantation, purple stars indicate cystometric measurements (CMG), and euthanasia. Bladder tissues were collected for histological analysis and western blotting after euthanasia.

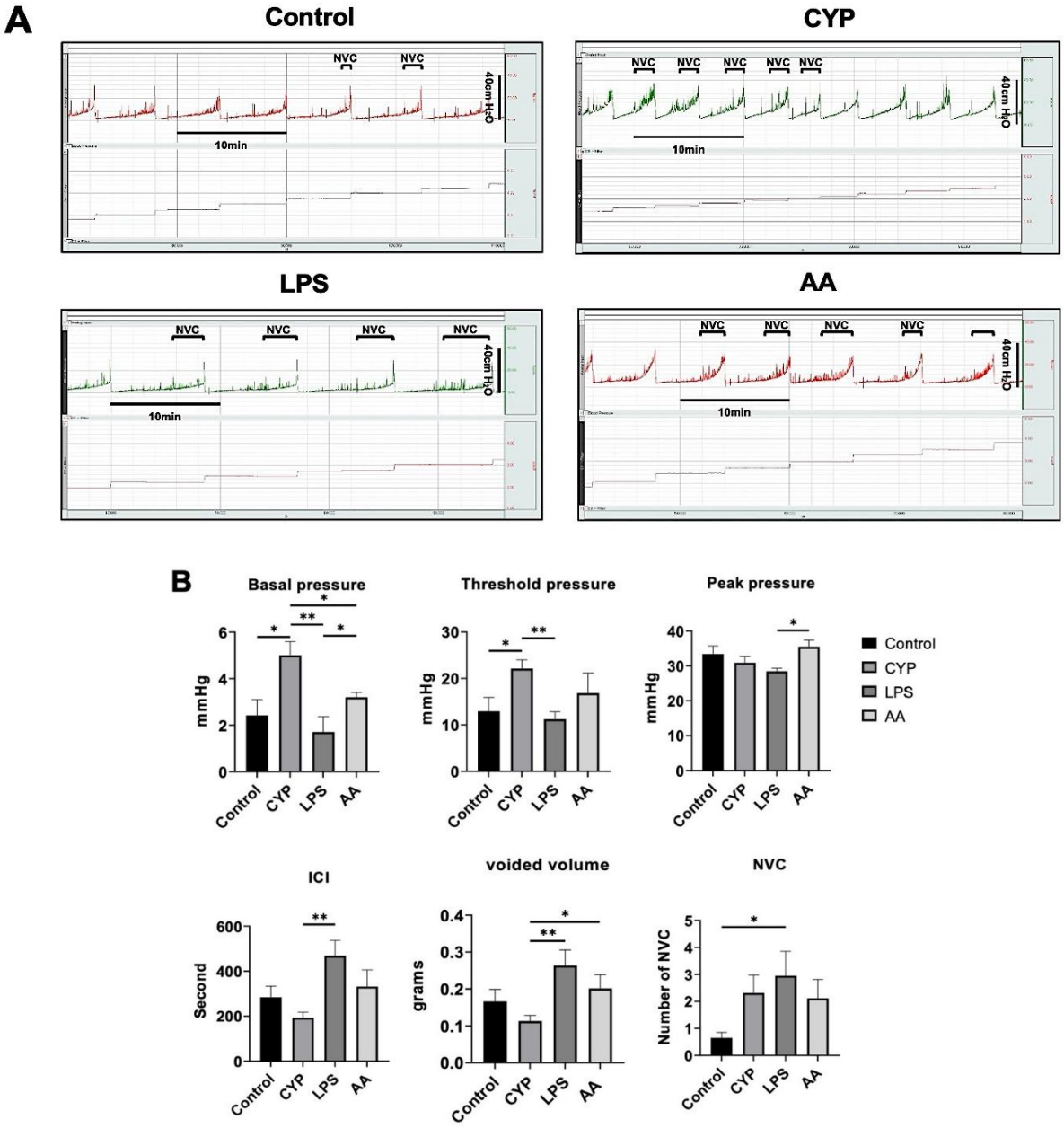

Figure 2. Evaluation of bladder function via cystometry in chemically induced IC mouse models

(A) Representative CMG tracings from NC-, cyclophosphamide CYP-, lipopolysaccharide LPS-, and acetic acid AA-treated mice. Tracings demonstrate voiding cycles and non-voiding contractions of NVCs over a 10-minute period. The AA- and CYP-treated groups showed increased pressure amplitudes and frequent NVCs, indicative of detrusor overactivity. (B) Quantitative analysis of CMG parameters across the groups. AA-treated mice exhibited significantly elevated peak pressure ($p < 0.05$), increased voided volume, and higher NVC frequency than controls, consistent with bladder overactivity. The intercontraction interval (ICI) was significantly prolonged in the LPS group, while the basal and threshold pressures were markedly increased in the CYP group. Data are presented as the mean ± SD ($n = 8$ per group); $p < 0.05$, $p < 0.01$, versus the control group, as determined by one-way ANOVA followed by Scheffé's post hoc test.

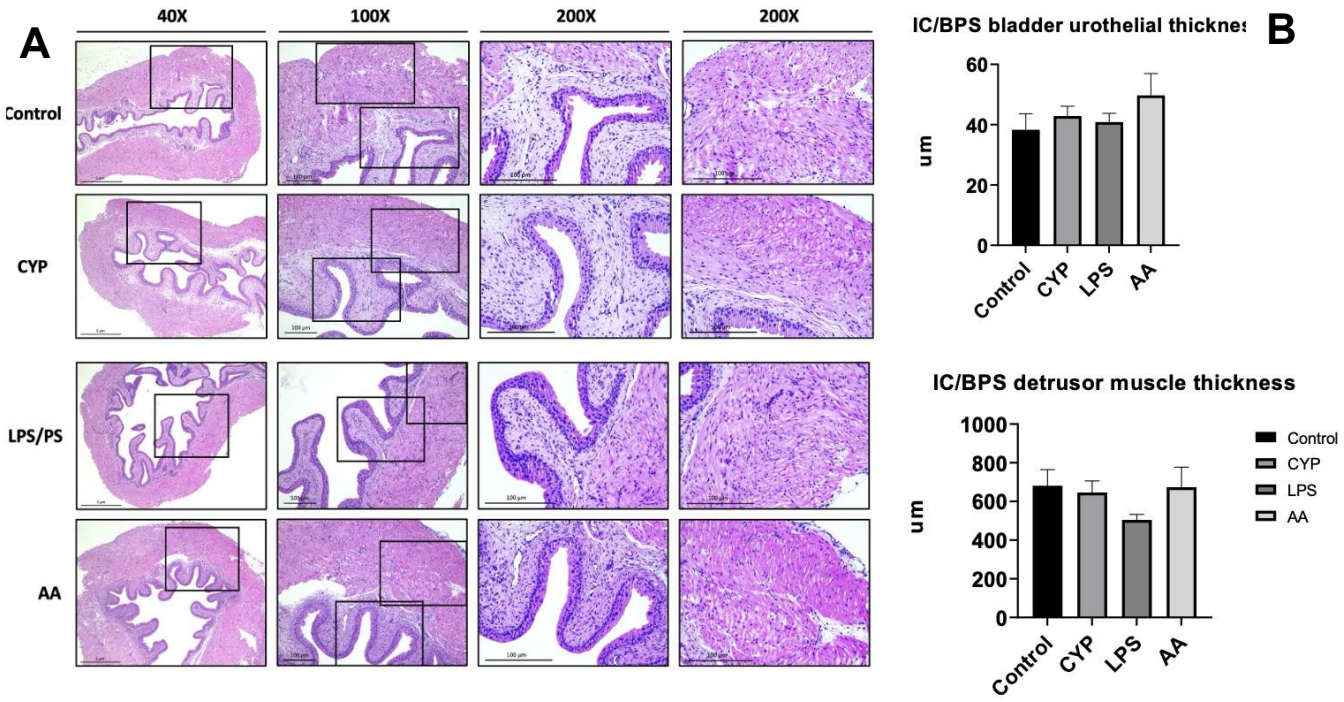

Figure 3. Histological and quantitative assessment of bladder pathology in ic mouse models

(A) Representative H&E-stained bladder sections from each experimental group (Control, CYP, LPS, AA) at 40×, 100×, and 200× magnifications. The AA-treated bladders exhibited severe urothelial hyperplasia, lamina propria edema, and detrusor muscle hypertrophy, indicative of chronic bladder inflammation. The LPS and CYP models showed moderate and focal changes, respectively, while the control tissues remained histologically intact. (B) Bar graphs represent the mean ± SD of urothelial and detrusor muscle thickness across all groups (n = 4 per group). The AA group showed the most significant increases in both parameters compared with the other groups, reinforcing its suitability as a model for chronic IC/BPS. Statistical comparisons were performed using one-way ANOVA followed by Scheffé post hoc test; *$p < 0.05$ was considered significant.

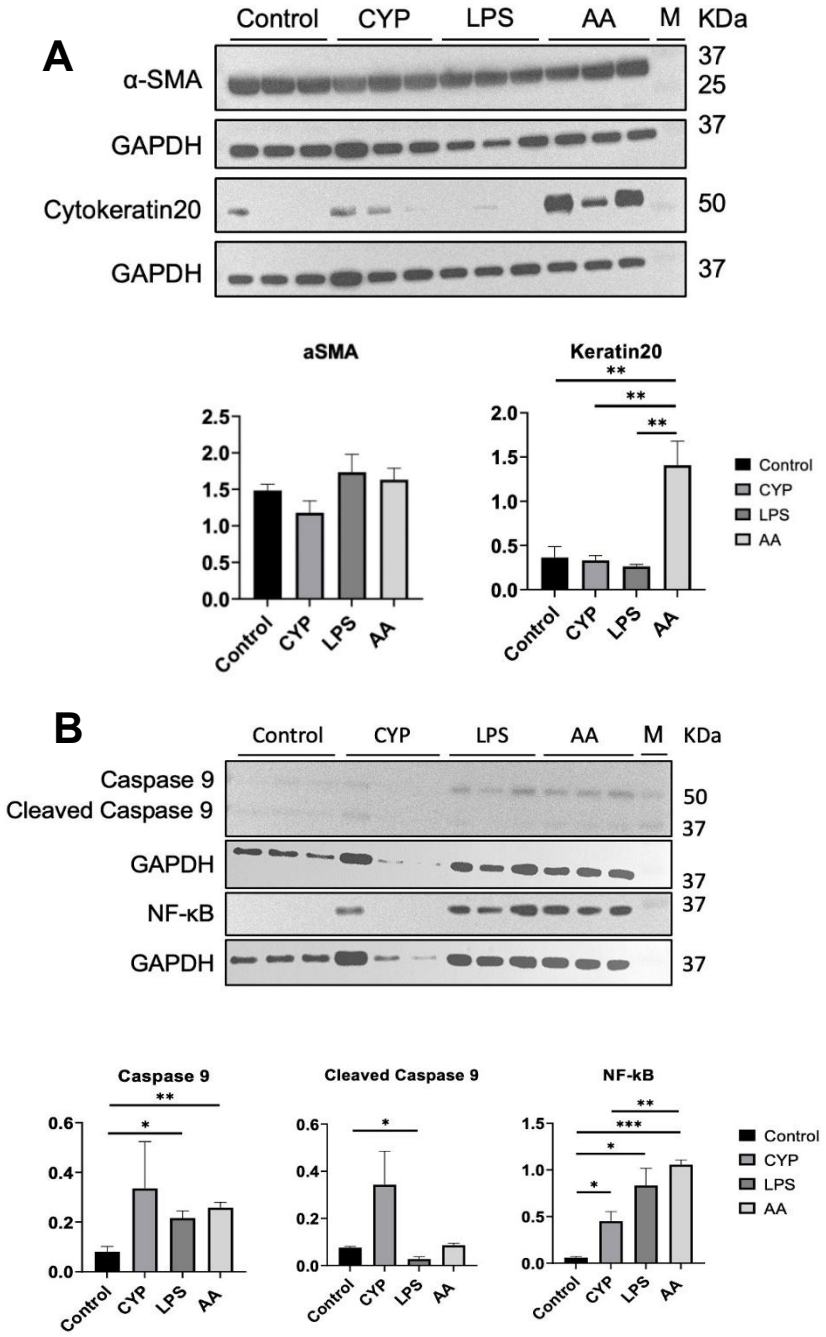

Figure 4. Protein expression profiling of structural, apoptotic, and inflammatory markers in bladder tissues of experimental interstitial cystitis models

(A) Representative Western blot images and densitometric quantification of α-SMA and cytokeratin 20 expression in mouse bladder tissues across the control, CYP-, LPS-, and AA-induced IC groups. GAPDH was used as an internal loading control. Cytokeratin 20 levels were significantly increased in the AA group, suggesting enhanced urothelial remodeling. (B) Western blot analysis and quantification of apoptotic and inflammatory markers caspase-9, cleaved caspase-9, and NF-κB. The CYP group exhibited the highest levels of caspase activation, whereas NF-κB was strongly up-regulated in the LPS and AA groups. Values are presented as the mean ± SD (n = 4). *p < 0.05, **p < 0.01, ***p < 0.001.

Establishing standardized murine models of intestial cystitis: comparative insights from lipopoly saccaride, acetic acid, and cyclophosphamide exposure

間質性膀胱炎標準化小鼠模型建立：比較脂多醣、醋酸與環磷酰胺暴露之差異

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中文摘要

背景：間質性膀胱炎（IC）是一種慢性膀胱疾病，其特徵為骨盆疼痛、頻尿及尿急，但無明確感染因素。化學誘導的動物模型對於探討 IC 之病理機制至關重要，然而，針對不同誘導劑的標準化比較性研究仍然稀少。**方法：**本研究比較三種常用之化學誘導 IC 模型，包括脂多醣體（LPS）、醋酸（AA）及環磷醯胺（CYP），使用雌性 C57BL/6 小鼠（n = 32，8 隻/組）。評估膀胱動力學參數包括基底壓力、閾值壓力、最大排尿壓力、膀胱收縮間期（ICI）及非排尿性收縮（NVCs）。膀胱組織經蘇木精-伊紅（H&E）染色進行組織學分析，並透過蛋白質免疫轉漬法（Western blot）測定 caspase-9、NF-κB 及細胞角蛋白 20（CK20）之表現量。**結果：**AA 組小鼠顯示最嚴重之尿路上皮破壞，其 caspase-9（3.1 倍）及 NF-κB（2.8 倍）表現顯著升高，CK20 表現則顯著降低（$p < 0.05$）。功能上，AA 組之 ICI 顯著縮短（82.4 ± 10.1 秒），且 NVCs 增加。LPS 組則顯示 ICI 延長（161.3 ± 8.9 秒）並伴隨中度發炎反應；CYP 組則觀察到基底壓力上升（14.7 ± 1.6 cmH_2O）及 NVCs 增加，反映膀胱逼尿肌過度活躍現象。**結論：**在所有測試模型中，AA 誘導之 IC 模型呈現最一致且明顯之發炎、組織學及功能性病變，適合用於探討上皮損傷與急性膀胱發炎相關之研究。此研究建立一套標準化比較框架，有助於未來進行 IC 轉譯性研究之模型選擇。

關鍵字：間質性膀胱炎、小鼠模型、膀胱動力學、發炎、醋酸、NF-κB

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Original Research Article

Applying Andersen's Behavioral Model to Explore the Long-Term Care Needs of Patients with Colorectal Cancer

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ABSTRACT

Background: Colorectal cancer is among the most prevalent malignancies, and increasing complexity in treatment and care delivery has heightened demand for long-term care (LTC) services. This study aimed to investigate LTC needs among colorectal cancer patients and analyze the influencing predisposing, enabling, and need-related factors based on Andersen's Behavioral Model of Health Services Use. ***Materials and methods:*** A cross-sectional survey was conducted from January 4 to June 8, 2024, at a regional hospital in New Taipei City, Taiwan. A total of 90 patients were enrolled, and data were collected using validated demographic and LTC needs questionnaires. Statistical analyses were performed using SPSS 29.0. ***Results:*** The average age of patients was 63.63, with 58.9% male and 92.2% fully independent in daily living functions. The most clearly recognized LTC need was "family caregiver support," while institutional care had the highest perceived need and willingness to use. Key predictors included age, employment status, living arrangement, economic condition, primary caregiver status, number of LTC information sources, use of assistive devices, disability level, specific care (e.g., port-A catheter care), and the number of LTC considerations. ***Conclusion:*** Patients exhibited moderate clarity and perceived need for LTC services but showed low willingness to use them. Family caregiver support and institutional care were notably preferred and influenced by multiple Andersen Model factors. These findings offer valuable implications for future LTC poli-

cy development and resource optimization, helping to bridge the gap between care awareness and actual utilization.

Keywords: Colorectal cancer, Long-term Care, Andersen's behavioral model of health services.

INTRODUCTION

Cancer has remained the leading cause of death in Taiwan since 1982. Over the past decade, the number of cancer-related deaths has increased by an average of 3.1% per year, reflecting the rising proportion of elderly individuals and population growth. Among the ten leading causes of cancer mortality, colorectal cancer ranks third, following lung and liver cancer. It has demonstrated a continuous upward trend in incidence, reinforcing its significance as a major public health concern[1]. According to incidence statistics, colorectal cancer has remained the most prevalent cancer among men in Taiwan for nearly 20 years, while ranking second among women, following breast cancer[1].The U.S. Centers for Disease Control and Prevention reported that in 2018, colorectal cancer ranked fourth in both cancer mortality and incidence in the United States, highlighting its significant global health impact[2].

Recognizing the importance of early detection, the Taiwanese government initiated a national cancer screening program in 2010, including fecal occult blood tests for colorectal cancer. This screening method has been shown to reduce colorectal cancer mortality by 23% and significantly improve early detection rates, leading to a five-year survival rate exceeding 90%[3]. However, despite advancements in medical technology and extended life expectancy, cancer has transformed into a chronic disease requiring long-term management. This shift has introduced complex challenges, including rising healthcare costs, the emergence of new pharmaceuticals, diversified treatment approaches, and increasing psychosocial distress, particularly among younger patients[4]. The rapid evolution of cancer therapies, combined with the increasing longevity of patients, has contributed to the growing complexity of colorectal cancer treatment and care models. These changes have intensified long-term care (LTC) needs, posing significant challenges to healthcare resource allocation and patient quality of life. Failure to adequately address these LTC demands may exacerbate the burden on healthcare systems, ultimately affecting patient survival outcomes[5-7].

The adverse effects of cancer treatment vary across disease types and therapeutic regimens, resulting in distinct physiological symptoms and psychosocial challenges. Consequently, cancer patients require multifaceted care strategies that encompass medical, psychological, and social domains[5]. LTC has become an increasingly critical component of oncology care, reflecting the evolving needs of cancer patients. Globally, LTC has emerged as a key healthcare priority, with Taiwan continuously refining its LTC policies to provide holistic, patient-centered, and integrated care services. The LTC 2.0 policy, introduced in 2017 under the LTC Services Act, seeks to foster aging in place while offering comprehensive and continuous care solutions[8]. The enactment of the LTC Services Act in 2015 further strengthened Taiwan's LTC infrastructure, facilitating the expansion of LTC centers and the integration of various service networks to improve resource accessibility for cancer patients[9-10].

As a family caregiver of a colorectal cancer patient, the researcher has firsthand experience of the emotional and physical toll that cancer imposes. While medical advancements have extended survival times, the prolonged uncertainty of disease trajectories places substantial psychological and logistical burdens on both patients and caregivers. The increasing complexity of daily life, including challenges related to nutrition, transportation, and financial stability, further exacerbates caregiver stress[11]. Unaddressed caregiver burden may negatively affect patient adherence to treatment plans and overall well-being, subsequently diminishing the family's ability to cope with the illness. This decline in patient and caregiver resilience can lead to reduced treatment compliance and impaired quality of life, highlighting the urgent need for enhanced LTC services[12-13]. Despite the implementation of LTC 2.0, significant gaps remain in the availability of practical LTC solutions for colorectal cancer patients[14].

To systematically analyze LTC needs and accessibility challenges faced by colorectal cancer patients, this study employed Andersen's Behavioral Model of Health Services. As one of the most widely applied theoretical frameworks in healthcare utilization research, Andersen's model incorporates three key do-

mains: predisposing factors, enabling factors, and need factors. This model sought to predict healthcare service utilization behaviors by examining individual and familial determinants[15-17].

Despite the growing prevalence of colorectal cancer, existing research on LTC experiences among these patients remains limited in Taiwan. Most studies focus primarily on treatment modalities and pharmaceutical development rather than LTC requirements. Given the increasing incidence of colorectal cancer and the escalating LTC burden associated with it, this study applied Andersen's Behavioral Model to investigate LTC needs, uncover key accessibility barriers, and generate actionable insights for optimizing LTC resources and clinical care practices.

MATERIALS AND METHODS

This study adopted a cross-sectional research design, using a structured questionnaire to collect data.

Participants and Sampling

This study employed a cross-sectional research design, utilizing a structured questionnaire to collect data from colorectal cancer patients receiving outpatient or inpatient care at a regional teaching hospital in New Taipei City, Taiwan. The survey was conducted from January 4 to June 8, 2024, with a total of 90 valid questionnaires collected. Participants were selected using a convenience sampling method, and eligibility criteria included a physician-confirmed diagnosis of colorectal cancer, age 18 or older, malignancy confirmed by pathology for at least six months, and the ability to communicate in Mandarin or Taiwanese. Patients diagnosed with multiple types of cancer or undergoing intubation or emergency treatment were excluded. Before data collection, the researcher explained the study's purpose and procedures to eligible participants and obtained written informed consent. Participants completed the questionnaire independently or with assistance from the researcher in outpatient consultation rooms or inpatient discussion rooms, with an average completion time of 15 to 20 minutes. Using G*Power software with an effect size of 0.3, a significance level of 0.05, and a power of 0.80, the minimum sample size required was 82; to account for potential attrition, a total of 90 valid samples were ultimately collected.

Theoretical Framework and Instruments

This study adopted Andersen's Behavioral Model as its theoretical foundation to analyze patient care behaviors. The model emphasizes the dynamic interaction of three primary components-predisposing factors, enabling factors, and need factors-offering a structured methodology for examining healthcare utilization and the underlying motivations driving patient decisions. In this study, variables were categorized as follows:

Predisposing Factors: Age, sex, marital status, education level, religion belief, Employment status, and living status.

Enabling Factors: Economic status, welfare identity, source of income, commercial insurance, primary caregiver, and sources of LTC information.

Need Factors: Self-rated health status, colorectal cancer condition, past care experience, and consideration factors for LTC use.

Dependent Variables: Clarity, perceived need, and willingness to use four types of LTC services (Figure 1).

The questionnaire was developed based on a review of relevant literature and expert consultation, with a content validity index (CVI) of .93, as assessed by three domain experts. It consisted of two main sections. The first section captured demographic and disease characteristics, including age, gender, marital status, education level, religious belief, occupation, living arrangement, and disease-related variables. The second section, the LTC Needs Scale, assessed patients' clarity, perceived need, and willingness to use four types of LTC services: Home-based care (1.Nutritional meal delivery, 2.Transportation services, 3.Home-based Medical care, 4.Home nursing, 5.Home visit by pharmacists, 6.Home visit by nutritionists, 7.Home-based rehabilitation, 8.Home service, 9. Assistive device rental, and 10.Living environment modification, etc.), Community-based services (Adult foster care, Day care services, Group homes, Respite care, and Community-based care centers, etc.), Institutional care (Retirement homes, Residential care facilities, Services for persons with disabilities, Veterans' homes, and Nursing homes, etc.), and Family caregiver support (Information provision and referral services, LTC knowledge/skills training, In home respite care, Emotional support and referral to group services, etc.). The scale demonstrated strong internal consistency reliability, with a Cronbach's α of .91, indicating good validity and reliability.

Data Analysis

All data were analyzed using SPSS version 29.0. Descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to summarize participant characteristics and distributions of LTC needs. For inferential analysis, t-tests was applied to compare differences in LTC needs across variables, while Pearson's correlation coefficient (r) and multiple regression were used to assess relationships between variables.

Ethical Considerations

This study received approval from the Institutional Review Board (IRB) of the regional hospital in Taishan District, New Taipei City (Approval No. FJUH112325). All participants provided written informed consent prior to participation. Data will be retained for two years after study completion and destroyed securely in accordance with personal data protection regulations to ensure participant confidentiality and data security.

RESULTS

A total of 90 valid questionnaires were collected, achieving a 100% response rate. The results revealed LTC needs among patients with colorectal cancer. Using Andersen's Behavioral Model, the study analyzed the predisposing, enabling, and need factors that influence LTC demand.

LTC Needs of Patients with Colorectal Cancer

Comparison of LTC Types

This study assessed clarity, perceived need, and willingness to use four LTC categories: home care, community care, institutional care, and family caregiver support. Comparative analysis revealed distinct preference patterns (Table 1).

Participants recognized family caregiver support the most, followed by institutional care, community-based care, and finally home-based care. In terms of perceived need, institutional care ranked highest, followed by community-based care, family caregiver support, and home-based care. Likewise, willingness to use LTC services followed the same order, with institutional care being the preferred option, while home-based care ranked lowest (Table 1).

When converted to a 100-point scale, the mean clarity score was 60.75, perceived need was 64.25, and willingness to use was 50.40(Table 1). These findings suggest that while participants demonstrated moderate clarity and need for LTC services, their actual willingness to utilize these services remained low, particularly for home and community-based LTC. This discrepancy between recognition and action indicates a gap in service utilization, warranting policy interventions and patient education.

a. Home-based Care

Only 8.9% had utilized home-based care services. Clarity of home-based care was lowest among all LTC types, with 47.8% reporting "Unclear" and a mean clarity score of 2.39 (SD = 0.71). Perceived need was slightly higher (2.51, SD = 0.67), while willingness to use home-based care remained low (2.43, SD = 0.82), marking it as the least preferred LTC option (Table 1).

The mean scores of clarity, perceived need, and willingness to use across LTC services were summed to represent overall LTC service demand, which served as the dependent variable in a stepwise regression analysis. For home-based care, significant predictors included the number of LTC consideration factors, being the primary caregiver, and economic status, explaining 25.1% of the variance (Table 4).

b. Community-based Care

Only one participant (1.1%) had utilized respite care. Clarity was limited, with 42.2% reporting "Unclear" (mean = 2.41, SD = 0.76). Perceived need had a mean score of 2.57 (SD = 0.62), and willingness to use was 2.50 (SD = 0.78) (Table 1).

Significant predictors of community-based care included the number of LTC consideration factors, being the primary caregiver, economic status, and age, collectively accounting for 20.8% of the variance (Table 4).

c. Institutional Care

None of the participants (100%) had previous institutional care experience. Institutional care had the highest perceived need among LTC types (mean = 2.69, SD = 0.65). Clarity was moderate (mean = 2.46, SD = 0.67), yet 81.1% of participants were either "uncertain" or "unwilling" to use this service (Table 1).

Significant predictors of institutional care included the number of LTC consideration factors, being the primary caregiver, and the use of assistive devices, collectively accounting for 19.5% of the variance (Table 4).

d. Family Caregiver Support

Only one patient (1.1%) reported experience using family caregiver support services,

specifically for information provision/referral, emotional support, and referral to group-based services. This service type exhibited the highest clarity among LTC options (mean = 2.48, SD = 0.72). Perceived need and willingness to use were both moderate (mean = 2.51, SD = 0.75) (Table 1).

Significant predictors of family caregiver support included the number of LTC consideration factors and being the primary caregiver, collectively accounting for 18.5% of the variance (Table 4).

Findings Based on Andersen's Behavioral Model Factors

Predisposing Factors

Among respondents, 58.9% were male and 41.1% were female. The age ranged from 37 to 83 years, with a mean age of 63.63 (SD = 9.50). More than half (51.1%) were under the age of 65. Most participants were married (71.2%), held a high school or vocational education level (36.7%), and identified with Taoism (34.5%). Regarding employment, 33.3% were retired, while 88.9% lived with others. The most common co-resident structure was one additional household member (32.2%).

Among predisposing factors, unemployed individuals demonstrated greater clarity regarding both home-based care (t = 2.045*) and institutional care (t = 2.410*). Those living alone also exhibited greater clarity of institutional care (t = 2.266*) (Table 2). Age was positively correlated with LTC perceived need across all categories (Table 3), and was also identified as a significant predictor of demand for community-based services (Table 4).

Enabling Factors

The majority of participants reported their financial status as "average" (57.8%). All respondents held a catastrophic illness certificate (100%). The primary source of income was self-funded (62.2%), while 55.6% had commercial insurance. The main caregiver was self (44.4%). Regarding LTC information, 64.4% of participants had access, primarily through media sources (40%).

Among enabling factors, individuals with lower economic stability showed significantly higher clarity regarding home-based care (t = -2.266*) and caregiver support (t = -2.676*). Economic status was also a significant predictor for both home-based care and community-based services (Table 4). Institutional care clarity differed significantly based on the presence of LTC information sources (t = 2.499*), while self-caregivers reported significantly higher clarity for home-based care services (t = 2.101*) (Table 2). This factor was also a significant predictor across all LTC service categories (Table 4). The number of LTC information sources available to patients was positively correlated with institutional care clarity (r = .257*) (Table 3).

Need Factors

Self-rated health status was predominantly "average" (61.1%), with a mean score of 3.08 (SD = 0.72). The average disease duration was 1.82 years (SD = 1.99), ranging from one month to over six years, with most patients (68.9%) diagnosed within the past year. The most common cancer stage was Stage III (50%). The majority of participants (92.2%) were fully independent in activities of daily living (ADL). All participants had undergone chemotherapy and port-A catheter care, with 16.7% receiving colostomy care. However, only 8.9% had used assistive devices, with wheelchairs being the most utilized. Regarding LTC -related considerations, 96.7% of participants had thought about LTC, with economic concerns (61.1%) and self-care ability (60%) as the most cited factors.

Among influencing factors, individuals who were fully independent demonstrated greater perceived need for institutional care (t = 2.384*). Patients receiving only Port A catheter care reported higher perceived need for family caregiving support (t = 2.384*). Participants who used assistive devices reported significantly higher perceived needs for home-based (t = 2.299*), community-based (t = 2.157*), and institutional (t = 2.669**) LTC services. Their willingness to use community-based (t = 2.431*) and institutional (t = 2.822**) services was also significantly greater (Table 2). Moreover, the use of assistive devices was identified as one of the predictors for institutional service demand (Table 4). The number of LTC consideration factors was positively correlated with both perceived need for LTC services and willingness to use them (Table 3). The number of LTC consideration factors was also a significant predictor across all LTC service categories (Table 4).

DISCUSSION

Analysis of the LTC Needs among Colorectal Cancer Patients

Findings from this study indicated that colorectal cancer patients exhibited low utilization rates across all four categories of LTC

services-home-based care, community-based care, institutional care, and family caregiver support. Despite moderate levels of clarity, perceived need, and willingness to use these services, actual engagement remains limited. This aligns with previous research highlighting the importance of strengthening integrated, continuous care resources in oncology settings[11,18].

Among the four LTC types, home-based care had the lowest utilization rate (8.9%), with low scores in clarity, perceived need, and willingness to use. These findings support the perspective of Shih & Huang[19], who suggested that without structured interdisciplinary integration, services may fail to align with patient needs, thereby reducing engagement rates. Wang & Chen[20] further emphasized that enhancing patient trust, service accessibility, visit frequency, and service diversity could help increase home care utilization.

Community-based care services were utilized by only one respondent, indicating significant underutilization. Although 92.2% of patients were fully independent in activities of daily living (ADLs) and may not require day-care or community housing, ensuring timely access to respite care for caregivers remains critical in reducing caregiver burden[7].

In contrast, institutional care services exhibited relatively high levels of clarity and perceived need, suggesting that patients were somewhat familiar with available options. However, 81.1% of participants expressed uncertainty or unwillingness to use institutional care, likely reflecting cultural preferences for aging in place and receiving family-centered home care, which remained a strong tradition in Taiwan[20-21].

Among LTC services, family caregiver support was the most widely recognized, yet clarity scores were still moderate, equating to 62 out of 100 on a normalized scale. Prior research highlighted the critical role of caregiver health in patient outcomes[22]. Moreover, Altschuler et al.[11] assert that caregivers should be regarded as equally important as patients, advocating for comprehensive caregiver support systems to reduce caregiver burden and strengthen family resilience in cancer care.

Factors Influencing LTC Needs

This study, guided by Andersen's Behavioral Model of Health Services, examined the relationships among predisposing, enabling, and need factors in shaping LTC needs. The results indicate that certain factors within the three dimensions were significantly related to LTC needs.

1. Predisposing Factors of LTC Needs

Age was a key factor significantly associated with LTC perceived need and was also identified as a primary predictor of demand for community-based care services. Older patients exhibited higher perceived need across all four service categories, consistent with findings by Yang[23] and Lai et al. [21], which suggest that older adults tend to require more long-term support systems.

Regarding employment status, unemployed individuals demonstrated significantly higher clarity of both home-based care (t = 2.045*) and institutional care (t = 2.410*) compared to employed individuals. Further analysis revealed that unemployed individuals were generally older and had longer disease durations, leading to greater exposure to care resources and stronger motivation to explore service options. However, Lai et al.[21] found no direct correlation between employment status and LTC service usage, suggesting the need for further examination of interaction effects among related variables.

Living arrangements also played a role in LTC clarity. Individuals living alone exhibited significantly greater clarity of institutional care services than those living with others (t = 2.266*). This finding aligned with research by Luo et al. [24] and Yang[23], which noted that people living alone tend to have heightened crisis awareness, leading them to be more proactive in preparing for future care needs.

2.Enabling Factors of LTC Needs

Patients with lower economic stability demonstrated significantly higher clarity of LTC resources, and this factor emerged as a predictor of both home-based and community-based care needs. This may be attributed to their constrained personal resources, which heighten motivation to seek LTC services, aligning with findings from Kao et al.[25] and Tseng & Shih7.

Patients who simultaneously served as their own primary caregiver reported significantly higher perceived need for home care services (t = 2.101*), and this dual-role status emerged as a predictor of overall LTC needs. This finding suggested that individuals who occupy both care recipient and caregiver roles experience heightened demand for external support, aligning with the conclusions drawn by Lai et al.[21]

Regarding LTC information access, findings indicated that the number of LTC

information sources was positively correlated with institutional care clarity (r = .257*), suggesting that greater access to information enhances service recognition. Interestingly, participants without formal LTC information sources reported higher clarity of institutional care, likely due to informal information sources, such as peer discussions or online platforms. This observation aligned with Babitsch et al.[26] and Wu et al.[27], who suggest that information accessibility significantly impact healthcare service utilization.

3. Need Factors of LTC Needs

Participants who were fully independent in ADLs reported significantly higher perceived need for institutional care (t =2.384*). This may reflect proactive planning behavior rather than actual functional limitation, supporting the view of Babitsch et al.[26], who emphasize the link between subjective need and healthcare-seeking behavior.

Regarding special care contexts, patients who receive only Port A catheter treatment report a higher perceived need for family caregiving support (t =2.384*). This suggested that individuals with lower clinical care intensity may face physical discomfort or psychological stress in daily life without timely professional assistance, thereby increasing their reliance on family caregivers and heightening their subjective perception of familial support.

Regarding the use of assistive devices, the findings indicated that patients who did not use such equipment reported higher perceived needs and greater willingness to utilize LTC services. This factor also emerged as a significant predictor of institutional care needs, suggesting that individuals without assistive devices may have unmet care needs. Although Babitsch et al.[26] highlighted that those with specific medical conditions tend to use more healthcare services, patients without assistive devices may still require substantial attention to their care needs due to disease burden or psychological distress.

Finally, the number of LTC considerations was positively and significantly correlated with both perceived need and willingness to use all four LTC services, and it was the first significant predictor included in the regression model. This supports the theoretical assumptions of Andersen's model, reinforcing the idea that patients who factor in multiple aspects of LTC planning are more likely to recognize their needs and seek related services.

CONCLUSIONS

This study explored LTC needs among colorectal cancer patients and revealed the following insights:

1. Patients exhibited approximately 60% clarity and perceived need for various LTC services, including home-based, community-based, institutional care, and family caregiver support. However, their willingness to utilize these services remained lower, at approximately 50%, indicating a significant gap between awareness and actual engagement.

2. A notable finding was that patients' willingness to use family caregiver support services was significantly correlated with their clarity, perceived need, and willingness to use home-based, community-based, and institutional care services.

3. Based on Andersen's Behavioral Model, key predisposing factors significantly influencing LTC needs included age, employment status, and living status.

4. Significant enabling factors affecting LTC demand were identified as economic status, who served as the primary caregiver, and the number of LTC information sources.

5.Critical need factors influencing LTC demand included use of assistive devices, level of disability, specific care needs (only receiving Port-A catheter care), and the extent to which patients considered LTC factors and their count.

These findings underscore the necessity of targeted interventions to bridge the utilization gap and optimize LTC resource allocation for this patient population.

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FIGURE AND FIGURE LEGEND

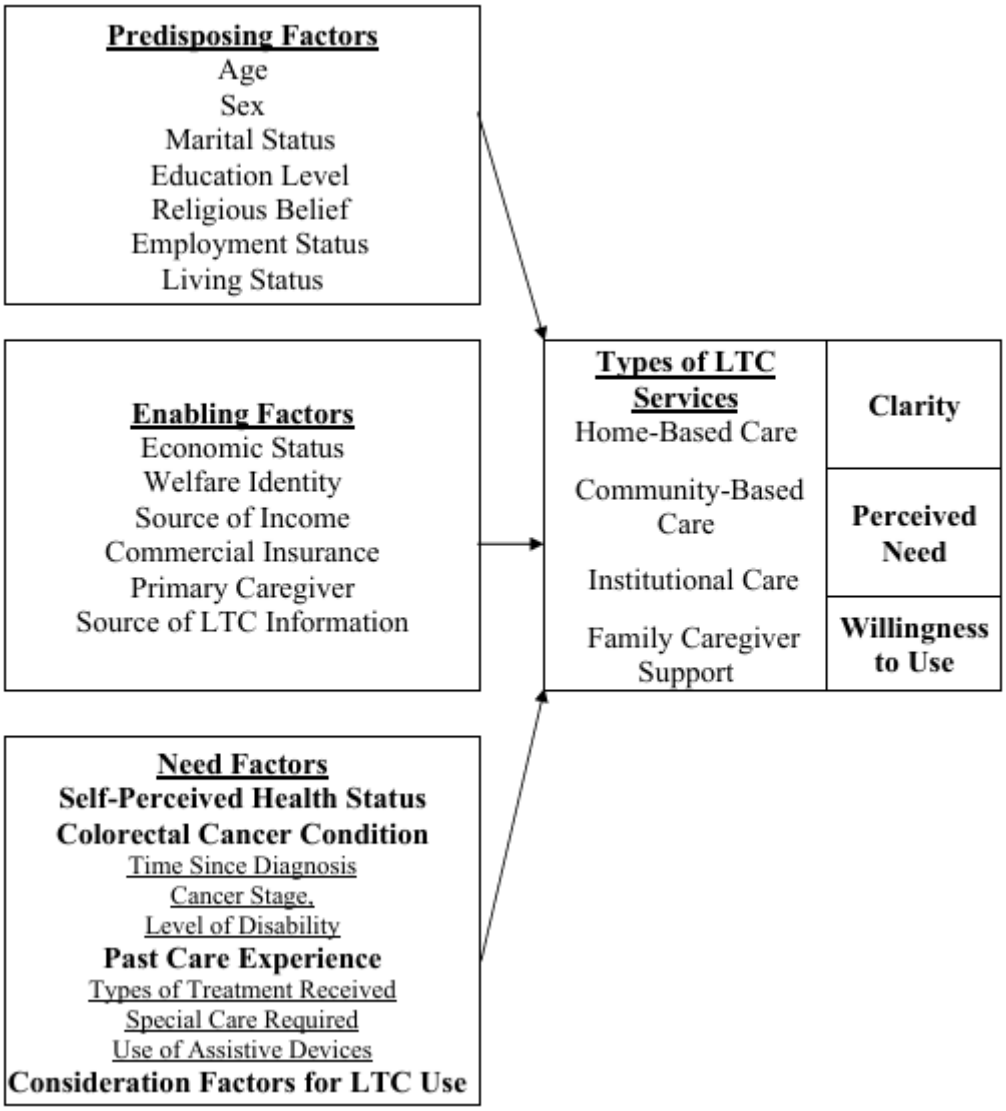

Figure 1. The theoretical framework of the study

TABLES

Table 1. Comparison of Clarity, Perceived Need, and Willingness to Use LTC Services (N = 90)

Service Type Overall mean	Evaluation Type	Clarity (M ± SD)	Perceived Need (M ± SD)	Willingness to Use (M ± SD)
Home-Based Care	Raw Score	2.39 ± .71	2.51 ± .67	2.43 ± .8
57.03	Converted Score (100-point)	59.75	62.75	48.60
Community-Based Care	Raw Score	2.41 ± .76	2.57 ± .62	2.50 ± .78
58.17	Converted Score (100-point)	60.25	64.25	50.00
Institutional Care	Raw Score	2.46 ± .67	2.69 ± .65	2.64 ± .84
60.52	Converted Score (100-point)	61.50	67.25	52.80
Family Caregiver Support	Raw Score	2.48 ± .72	2.52 ± .64	2.51 ± .75
58.40	Converted Score (100-point)	62.00	63.00	50.20
Overall Average	Raw Score	2.43 ± .64	2.57 ± .59	2.52 ± .72
58.47	Converted Score (100-point)	60.75	64.25	50.40

Note: Converted scores are based on a maximum of 4 points for clarity and need (converted by multiplying M × 25), and 5 points for willingness (converted by M × 20).

Table 2. Factors Influencing LTC Needs among Colorectal Cancer Patients (N = 90)

Factors		n	Home-Based Care	Community-Based Care	Institutional Care	Family Caregiver Support
			M±SD	M±SD	M±SD	M±SD
Clarity						
Employment Status	Unemployed	59	2.49± .75	2.51± .75	2.58± .67	2.54± .65
	Employed	31	2.19± .60	2.23± .76	2.23± .61	2.35± .63
	t(*p*)		2.045* (.044)	1.688(.950)	2.410* (.018)	1.173(.244)
Living Status	Alone	10	2.70± .67	2.70±1.06	2.90± .74	3.00± .67
	Not Alone	80	2.35± .71	2.38± .72	2.40± .65	2.41± .71
	t(*p*)		1.471(.145)	1.275(.206)	2.266* (.026)	2.495(.014)
Economic Status	Moderate	25	2.12± .73	2.24± .78	2.28± .74	2.16± .80
	Below Moderate	65	2.49± .69	2.48± .75	2.52± .64	2.60± .66
	t(*p*)		-2.266*(.026)	-1.325(.188)	-1.546(.126)	-2.676*(.019)
Source of LTC Information	None	32	2.53± .80	2.47± .88	2.69± .74	2.63± .79
	Yes	58	2.31± .65	2.38± .70	2.33± .60	2.40± .67
	t(*p*)		1.413(.161)	.530(.597)	2.499*(.014)	1.445(.152)
Primary Caregiver	Self	40	2.68± .73	2.70± .61	2.80± .65	2.65± .66
	Other	50	2.38± .60	2.46± .61	2.60± .64	2.42± .61
	t(*p*)		2.101*(.039)	1.853(.067)	1.466(.146)	1.712(.090)
Use of Assistive Devices	None	82	2.44± .67	2.44± .74	2.49± .63	2.51± .69
	Yes	8	1.88± .99	2.13± .99	2.13± .84	2.13± .99
	t(*p*)		2.177*(.032)	1.113(.269)	1.465(.147)	1.456(.149)
Perceived Need						
Independent	Fully	83	2.54± .63	2.59± .61	2.73± .63	2.55± .63
	Not Fully	7	2.14±1.07	2.29± .76	2.14± .69	2.14± .69
	t(*p*)		1.515(.133)	1.255(.213)	2.384*(.019)	1.649(.103)
Special Care Required	Only	69	2.58± .70	2.62± .62	2.77± .65	2.61± .65
- Port-A Catheter	Not only	21	2.29± .56	2.38± .59	2.43± .60	2.24± .54
	t(*p*)		1.770(.080)	1.583(.117)	2.147(.035)	2.384*(.019)
Use of Assistive Devices	None	82	2.56± .61	2.61± .58	2.74± .61	2.56± .61
	Yes	8	2.00±1.07	2.13± .84	2.13± .84	2.13± .84
	t(*p*)		2.299*(.024)	2.157*(.034)	2.669**(.009)	1.865(.066)
Consideration Factors	None	3	3.00± .00	3.00± .00	3.33± .58	3.00± .00
for LTC Use	Yes	87	2.49± .68	2.55± .62	2.63± .64	2.51± .65
	t		6.939***	6.698***	1.775	7.151***
	(*p*)		(.000)	(.000)	(.079)	(.000)
Willingness to Use						
Use of Assistive Devices	None	82	2.48± .79	2.56± .76	2.72± .81	2.57± .72

		8	2.00±1.07	1.88± .84	1.88± .84	1.88± .84
Yes						
	t(*p*)		1.576(.119)	2.431*(.017)	2.822**(.006)	2.581*(.012)
Consideration Factors		3	3.00± .00	3.00± .00	3.33± .58	3.33± .58
None						
for LTC Use		87	2.41± .83	2.48± .79	2.62± .84	2.48± .75
Yes						
	t		6.596***	6.104***	1.456	1.953
	(*p*)		(.000)	(.000)	(.149)	(.054)

*$p < .05$，**$p < .01$，***$p < .001$

Table 3. Correlation Analysis of LTC Needs among Colorectal Cancer Patients（N = 90）

Factors		Age	N I	N C	Home-Based Care (HBC)			Community-Based Care (CBC)			Institutional Care (IC)			Family Caregiver Support (FCS)	
r					C	P	W	C	P	W	C	P	W	C	P
HBC	**C**	-.066	.149	.015	1										
	P	.216*	.195	.367***	.329**	1									
	W	.191	.174	.395***	.207*	.610***	1								
CBC	**C**	.044	.056	.026	.858***	,286**	.179	1							
	P	.249*	.108	.286**	.208*	.832***	.550***	.239*	1						
	W	-.194	.119	.314**	.292**	.553***	.812***	.216*	.592***	1					
IC	**C**	.121	.257*	.145	.726***	.224*	.269*	.660***	.209*	.224*	1				
	P	.262*	.143	.274**	.119	.703***	.531***	.148	.781***	.466***	.174	1			
	W	.197	.122	.322**	.271**	.563**	.682***	.231*	.566***	.702***	.270*	.684***	1		
FCS	**C**	.040	.152	.085	.768**	.231*	.158	.700***	.142	.248*	.703**	.201	.265*	1	
	P	.219*	.156	.296**	.190	.806***	.612***	.131	.805***	.617***	.120	.831***	.622***	.183	1
	W	.105	.144	.382***	.337**	.630***	.800***	.276**	.625***	.877***	.289**	.537***	.718***	.290**	.675**

Note: $*p < .05$，$**p < .01$，$***p < .001$

NI=Number of LTC Information Sources NC= Number of Consideration Factors

C= Clarity P= Perceived Need W=Willingness to Use

Table 4. Stepwise Regression Analysis of LTC Needs among Colorectal Cancer Patients (N=90）

Factors	*B*	β	Adjed-R^2	*t*	VIF
Home care					
constant	6.526			9.4205***	
NC	.471	.311		3.281***	1.067
Primary Caregiver	-2.360	-.679		-3.995***	3.428
Economic Status	1.601	.463	.251	2.685**	3.528
Community services					
constant	3.975			3.008**	
NC	.341	.235		2.412*	1.070
Primary Caregiver	-2. 830	-.626		-3.583***	3.428
Economic Status	1.633	.493		2.775**	3.551
Age	.039	.227	.208	2.372*	1.029
Institutional care					
constant	6.469			9.753***	
NC	.394	.265		2.627**	1.127
Primary Caregiver	-.889	-.260		-2.732**	1.003
Use of Assistive Devices	1.316	.226	.195	2.241	1.125
Family caregiver support					
constant	8.024			20.758***	
NC	.502	.347		3.621***	1.002
Primary Caregiver	-1.021	-.307	.185	-3.201**	1.002

Note: * $p < .05$ ** $p < .01$ *** $p < .001$

NC= Number of Consideration Factors

Applying Andersen's Behavioral Model to Explore the Long-Term Care Needs of Patients with Colorectal Cancer

運用 Andersen 健康服務行為模式探討大腸直腸癌病患長期照護需求

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中文摘要

背景：大腸直腸癌是最常見一種癌症，隨治療日益複雜化及醫療照護模式改變，對長期照護服務的需求日益增加。本研究旨在調查大腸直腸癌患者的長期照護需求，並根據 Andersen 健康服務行為模式分析影響之傾向、使能和需求因素。**方法**：於 2024 年 1 月 4 日至 6 月 8 日在台灣新北市一區域醫院進行橫斷面調查。共收案 90 名病人，採經效度檢核的基本資料和長期照護需求問卷收集資料，以 SPSS 29.0 軟體進行資料分析。**結果**：患者平均 63.63 歲，58.9%為男性，92.2%能完全獨立完成日常生活活動。最明確的長照需求是「家庭照顧者支持照護」，而「機構服務」的需求和使用意願相對最高。影響長照需求的傾向因素包括年齡、職業和居住狀況；使能因素含經濟狀況、主要照顧者和長期照護訊息資訊來源數量；需求因素則有無使用輔具、失能程度、特殊照護（僅/不僅接受人工血管護理者）及有無使用長期照護考慮因素及其數量。**結論**：本研究顯示區域醫院的大腸直腸癌患者對長照服務有中等的清楚與自覺需求程度，但使用意願存在落差。其中，家庭照顧支持和機構服務的需求與意願較為突出，這些受 Andersen 模式之傾向、使能與需求等多重因素影響。本研究結果可為未來長照政策制定與資源優化提供依據，以縮小患者認知與實際利用間之差距。

關鍵字：大腸直腸癌、長期照護、Andersen 健康服務行為模式

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Case Report

A Case Report of Congenital Urachal Cyst in a Newborn with Unusual Presentation Mimicking an Umbilical Cord Hernia

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ABSTRACT

Introduction: The umbilicus is a common site of various embryological anomalies. Congenital umbilical cord hernia involves the herniation of abdominal contents into the umbilical cord, a condition often misdiagnosed as omphalocele. ***Case Presentation:*** We describe a rare case of a term male neonate with a prenatal diagnosis of an umbilical cyst. Postnatally, the cyst ruptured, revealing exposed viscera with a blood-tinged discharge. Initial suspicion of congenital umbilical cord hernia led to imaging studies, which ruled out other gastrointestinal or genitourinary anomalies. Surgical exploration confirmed a urachal cyst, which was excised without complications. The patient had an uneventful recovery and was discharged in good condition. ***Discussion:*** Urachal cysts, though uncommon, can mimic other umbilical anomalies and may present atypically, as seen in our case. Early diagnosis and prompt surgical intervention are essential to prevent complications. This case emphasizes the diverse presentations of urachal remnants and the importance of clinical suspicion in managing umbilical anomalies. ***Conclusion:*** Urachal cysts can present as umbilical cord hernias, complicating diagnosis. A thorough clinical evaluation, imaging, and surgical management are critical to ensuring favorable outcomes.

Keywords: Umbilical cyst, Urachus, Urachal cyst, Umbilical cord hernia

INTRODUCTION

Psoriasis is a chronic inflammatory dermatosis, which is a systemic disorder associated with arthritic, psychological, cardiovascular. The umbilicus is a common site of various embryological anomalies involving the midgut, abdominal wall, vessels, and urachus. Umbilical cord hernia is a distinct condition that arises during a specific stage of embryological development.[1] Congenital umbilical cord hernia involves herniation of the small bowel and occasionally other abdominal contents into the umbilical cord.[2,3] Therefore, any prenatal or postnatal finding of an umbilical mass requires careful evaluation.

Literature review reveals limited reports of umbilical cord hernia associated with extracelomic colonic atresia, short gut, and patent omphalomesenteric duct.[4,5] Few cases describe umbilical cord swelling or cord cysts linked to a patent urachus.[4]

We present a rare case of a term neonate diagnosed with a urachal cyst presented with umbilical cord hernia, covered by viscera, without a fistulous tract. This report highlights the unique clinical features and diverse presentations of urachal remnants in neonates.

CASE REPORT

A term male newborn, weighing 2670 g, was born via spontaneous vaginal delivery at 40 weeks of gestation. Prenatal examination revealed no significant anomalies, except for a suspected cyst in the umbilical region. After birth, a 1.5 × 1.5 cm umbilical cyst was observed, and routine care was provided at a regional obstetrics and gynecology clinic. Five days after birth, the umbilical cyst ruptured, revealing exposed viscera with a mild blood-tinged discharge (Figure 1). The baby was subsequently transferred to our ward for further management.

Initially, the patient was suspected to have congenital hernia of the umbilical cord associated with a small omphalocele. We covered the mass with warm saline-soaked gauze, administered intravenous fluids, and started prophylactic antibiotics. Comprehensive imaging studies—including abdominal and renal ultrasonography—were conducted to thoroughly evaluate for any additional anomalies beyond the umbilical hernia and showing no gastrointestinal or genitourinary anomalies.

The patient remained vitally stable, and surgery was performed the following day. During the operation, a urachal cyst was confirmed (Figure 2). The urachus had failed to seal at its connection to the umbilicus, resulting in a blind-ending tract extending from the umbilicus into the bladder. The urachal cyst was excised, and the umbilical ring was closed. There were no intraoperative complications, and postoperative recovery was uneventful. Histopathological examination revealed a sinus tract lined with bland-looking transitional epithelium, consistent with a urachus with secondary infection. Feeding was initiated 24 hours postoperatively, and the patient was discharged in good clinical condition on the 7th postoperative day.

This study was approved by Institution-al Ethics Review Board (permission number: T-20241110).

DISCUSSION

Congenital hernia of the umbilical cord, also known as umbilical cord hernia, is a different type of ventral abdominal wall defect, in which the midgut is found herniating into the substance of the umbilical cord. Its incidence is estimated to be 1 in 5000.[6] Unlike omphalocele and gastroschisis, there is no deficiency of the anterior abdominal wall and is not linked chromosome anomalies. It originates at an early stage of embryogenesis and therefore may be detectable by fetal ultrasonography as early as the second trimester.[2] Congenital hernia of the cord is an often misdiagnosed and under-reported entity easily confused with a small omphalocele.[6]

In the differential diagnosis of umbilical cord hernia in neonates, it is crucial to distinguish this condition from other causes of umbilical protrusions for appropriate management. Umbilical cord hernia involves herniation of abdominal contents into the umbilical cord, covered by a thin membranous sac. In contrast, omphalocele presents with a similar herniation but is often larger and associated with a broader base and other congenital anomalies. Gastroschisis, another differential, is characterized by an abdominal wall defect without a membranous covering, typically located lateral to the umbilicus.[6]

Umbilical cysts should also be considered in the differential diagnosis of umbilical cord hernia. These cysts are uncommon, lined with epithelium, and arise from remnants of the omphalomesenteric duct or allantois.[7,8] Patent omphalomesenteric duct anomalies, including cysts and sinuses, result from the persistence of the vitelline duct and may involve intestinal structures, often presenting with gastrointestinal symptoms.[9] In contrast,

urachal cysts originate from incomplete obliteration of the urachus and are confined to the urinary tract, typically appearing as midline umbilical masses without intestinal involvement.[10] Accurate differentiation between these conditions requires careful clinical evaluation and imaging to ensure appropriate surgical management.

The urachus is a tubular structure that connects the cloaca to the allantois during fetal development, eventually forming the bladder and umbilicus. Normally, the urachus becomes obliterated during embryogenesis. Failure of this process can lead to urachal abnormalities, which are classified based on the persistence of the urachus between the bladder and umbilicus.[11] The incidence is approximately 1: 5000 livebirths.[12,13] These include patent urachus (47%), urachal cyst (30%), umbilical-urachal sinus (18%), and vesico-urachal diverticulum (3%).[10] In cases with a patent urachus or urachal abnormalities, the presentations vary from umbilical discharge to recurrent urinary tract infections and abdominal pain.

Our case differs from typical urachal anomaly presentations, where patent urachus is usually identified postnatally by urine leakage from the umbilicus. In contrast, this patient presented with a prenatal umbilical cyst resembling an umbilical cord hernia, without urine leakage or genitourinary symptoms. Unlike most reported cases where urachal cysts are diagnosed after secondary infection or symptomatic presentation, our patient was diagnosed and treated before significant complications. This highlights the need for increased clinical suspicion in similar cases and contributes to a broader understanding of the variable presentations of urachal remnants.

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FIGURE AND FIGURE LEGENDS

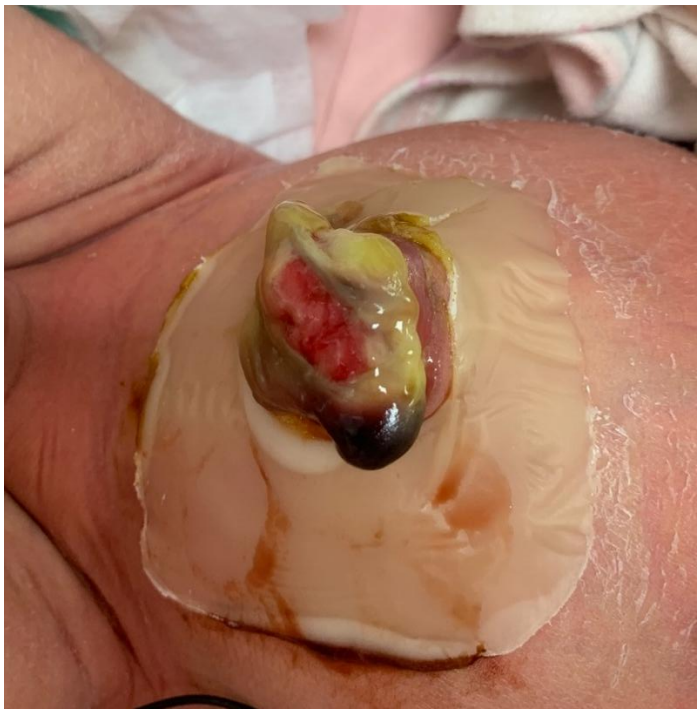

Figure 1. The viscera of umbilical cyst ruptured and mild blood-tinged discharged was found

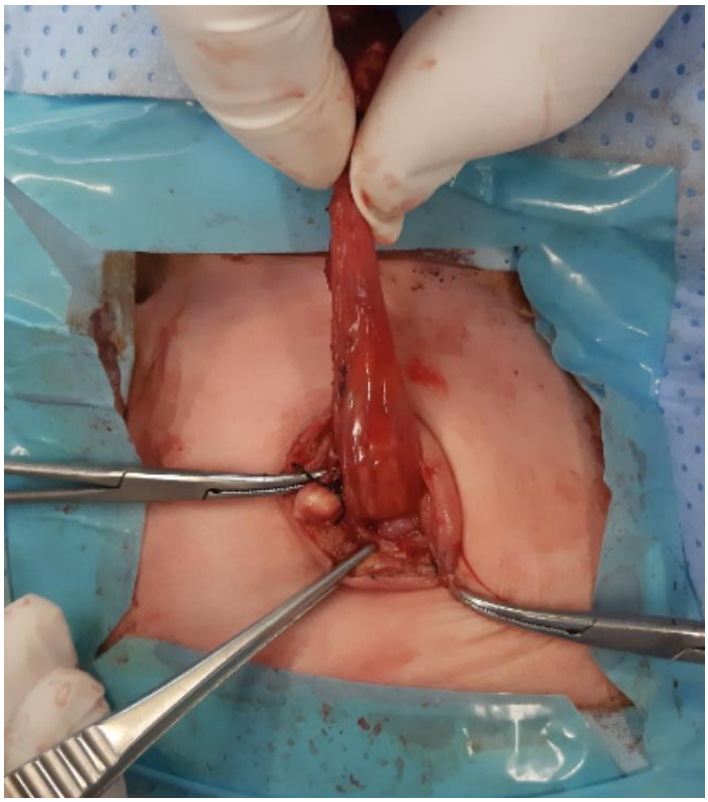

Figure 2. The urachal cyst was dissected, revealing that it did not seal close to the umbilicus and lead to a blind ending tract into the bladder.

A Case Report of Congenital Urachal Cyst in a Newborn with Unusual Presentation Mimicking an Umbilical Cord Hernia

新生兒先天性臍尿管囊腫以非常見臍腹壁疝氣表現：案例報告

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中文摘要

本病例報告介紹了一名在產前檢查中發現 1.5 x 1.5 公分先天性臍部囊腫的新生兒。最初懷疑為臍腹壁疝氣，因此進行了全面檢查，未發現其他相關的異常。在進行手術切除後，病灶被確診為先天性尿道囊腫。嬰兒對手術耐受良好，於術後第 7 天順利出院，未出現併發症。此病例強調了在新生兒臍部囊腫中進行鑑別診斷的重要性，臍尿管囊腫可能有類似其他臍部異常的臨床表現如臍腹壁疝氣。早期診斷和及時手術可降低感染的病發症。本病例強調了臍尿管遺跡的多樣性表現，以及在處理臍部異常時提高臨床懷疑的重要性。

關鍵字：臍部囊腫、臍尿管囊腫、臍腹壁疝氣

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Case Report

Fatal Case of Alcoholic Liver Cirrhosis Complicated by Tuberculosis Bacteremia: A Case Report

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ABSTRACT

We report a case of a 36-year-old male patient with alcoholic liver disease who was admitted due to fever and right upper limb swelling. During hospitalization, the patient was diagnosed with liver cirrhosis complicated by open pulmonary tuberculosis, Acinetobacter baumannii and tuberculous bacteremia. Despite aggressive treatment, including anti-tuberculosis medications and supportive care, the patient died due to multiple organ failure. This case highlights the diagnostic and therapeutic challenges of tuberculosis infection in cirrhotic patients and emphasizes the importance of early diagnosis and individualized treatment approaches.

Keywords: liver cirrhosis, tuberculosis bacteremia, acute respiratory distress syndrome

INTRODUCTION

Liver cirrhosis is a severe chronic condition that compromises the immune system, making patients more susceptible to various infections.[1] Open pulmonary tuberculosis, characterized by the presence of acid-fast bacilli in sputum microscopy or culture, represents a highly infectious form of the disease. These patients are capable of transmitting the infection to others through respiratory droplets, making early diagnosis and proper management crucial not only for the patient but also for public health.[2] Tuberculous bacteremia, the presence of Mycobacterium tuberculosis in the bloodstream, represents a severe form of disseminated tuberculosis. While relatively rare in immunocompetent individuals, its incidence increases significantly in immunocompromised hosts,[3] including those with the disease of acquired immunodeficiency syndrome and liver cirrhosis.[4,5] This case report describes a complex case of a cirrhotic patient with open pulmonary tuberculosis combine with bacteremia and was expired due to acute respiratory distress syndrome (ARDS). The reported mortality rate of tuberculous bacteremia ranges from 20% to 50%, with even higher rates in patients with underlying liver disease.[6,7] The combination of liver cirrhosis with tuberculosis bacteremia is rare and presents unique diagnostic and therapeutic challenges.[8] Liver dysfunction may mask typical symptoms of tuberculosis, while also limiting treatment options due to potential hepatotoxicity of first-line anti-tuberculosis medications.[9] By analyzing this case, we hope to raise awareness of such com-

plex situations and discuss the importance of diagnostic and treatment strategies.

CASE REPORT

A 36-year-old alcoholic liver cirrhosis male was sent to our emergency room due to fever with chillness and swelling in right upper limb for more than one week. Mild abdominal distension, liver and spleen palpable was also noted and abdominal ultrasound showed liver cirrhosis, ascites and splenomegaly. Under the impression of cellulitis and liver cirrhosis, he was admitted to our ordinary ward. During hospitalization, the patient presented with hyponatremia (Na: 129mmol/L), coagulopathy (PT 18.5 seconds, INR 1.6), thrombocytopenia (Platelets 38×10^9/L), liver dysfunction (ALT 56U/L, AST 78U/L, Albumin 28g/L) and hyperbilirubinemia (Total Bilirubin 6.7mg/dl). On day 3, the patient passed a significant amount of bloody stool, followed by a drop in hemoglobin to 3.7 mg/dL. The panendoscopy was performed and showed esophageal variceal rupture combied with active bleeding. Due to hypovolemic shock and persistent high fever, he was transferred to the intensive care unit (ICU). On day 4, followed chest X-ray (figure 1-C) showed bilateral lung edema and intubation with invasive ventilator was performed for acute respiratory failure. On day 9, extubation was performed and follow up CXR showed bilateral lung infiltration regress change. But intermittent high fever was still noted and an abdominal CT scan without contrast showed massive ascites, which was tapped, revealing clear yellowish fluid. Laboratory analysis indicated no signs of infection in the ascites. On day 25, Acinetobacter baumannii was isolated from sputum and blood culture. Positive acid-fast staining was also found from sputum and blood smear, thus pyogenic infection with sepsis, open pulmonary tuberculosis and tuberculosis bacteremia were suspected. On day 34, chest X-ray (figure 1-D) revealed bilateral peripheral infiltration and consolidation, and arterial blood gas showed metabolic acidosis with hypoxemia (pH:7.187 pCO2:14.3 mmHg pO2:68.6 mmHg HCO3 act:5.3 meq/L). Sepsis with acute respiratory distress syndrome was suspected and intubation was performed again. Unfortunately, the patient's condition got worsened rapidly, with hypoxemia, hypercaboncemia, hypotension, hypoglycemia and expired on day 36.

Review his history, the sputum study for tuberculosis was negative finding at initinal during this hospilization. He was even admitted to our hospital due to pneumonia with pleural effusion 3 years ago. (figure 1-A) At that time, sputum and pleural effusion study for tuberculosis was also negative finding. Two years ago, he suffered from a fever with a productive cough. Pneumonia was suspected, and there was no evidence of tuberculosis. (figure 1-B) Oral antibiotics were given for one week in the outpatient clinic.

This study was approved by Institution-al Ethics Review Board (permission number: CGH-P114039).

DISCUSSION

The diagnosis of pulmonary tuberculosis is primarily based on abnormalities observed in chest X-rays combined with sputum examinations.[10] The progression of tuberculosis is either chronic or subacute. In this case, the initial chest X-ray upon admission was normal, and the sputum acid-fast bacilli test was negative, indicating no signs of tuberculosis at that time. However, the patient subsequently developed cellulitis accompanied by persistent high fever, and chronic alcoholic liver cirrhosis led to complications such as massive esophageal variceal bleeding and acute pulmonary edema due to extensive fluid resuscitation, resulting in respiratory failure that required intubation and mechanical ventilation. Approximately one month after hospitalization, the patient experienced bacteremia due to Acinetobacter baumannii and Mycobacterium tuberculosis, sepsis, and acute respiratory distress syndrome. This experience highlights that the progression of tuberculosis in immunocompromised patients can be rapid[11]; therefore, when dealing with such patients, even if initial tests for tuberculosis are negative, we must maintain a high index of suspicion and vigilance regarding the possibility of tuberculosis.

Bacteremia from Mycobacterium tuberculosis is relatively rare and typically occurs in immunocompromised patients, such as those with HIV.[12] The patient in this case had alcoholic hepatitis, which inherently causes immune deficiency and malnutrition. Additionally, cirrhosis leads to impaired synthesis of immune factors and reduced toxin clearance, while accompanying splenomegaly can decrease the number of lymphocytes and other immune cells in the blood.[13] As a result, infections in these patients often present atypically and severely, with poorer prognosis, making early diagnosis and treatment even more critical.[14]

In treating pulmonary tuberculosis in patients with cirrhosis, the abnormal liver function restricts the use of some first-line tuberculosis medications, such as rifampin, isoniazid, and pyrazinamide.[15] Therefore, we used streptomycin

and levofloxacin to treat the tuberculosis, along with cefepime and meropenem for the Acinetobacter baumannii bacteremia.

Infections leading to sepsis and acute respiratory distress syndrome are associated with high mortality rates, and their prognosis is closely related to the patient's age, chronic diseases, immune deficiency, and the extent of organ failure.16 In this case, although the patient was young, the immune deficiency caused by end-stage cirrhosis and sepsis led to multiple organ failure, resulting in a poor prognosis. Currently, there are no effective specific treatments for sepsis; the only option is supportive therapy for the organs.17 However, due to the rapid progression and extensive impact of the disease, the patient unfortunately passed away.

CONCLUSION

For high-risk populations such as patients with liver cirrhosis, clinicians should maintain heightened awareness and consider tuberculosis screening promptly when symptoms like fever present. Early diagnosis not only improves patient outcomes but also prevents disease transmission, which has significant public health implications.

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FIGURE AND FIGURE LEGEND

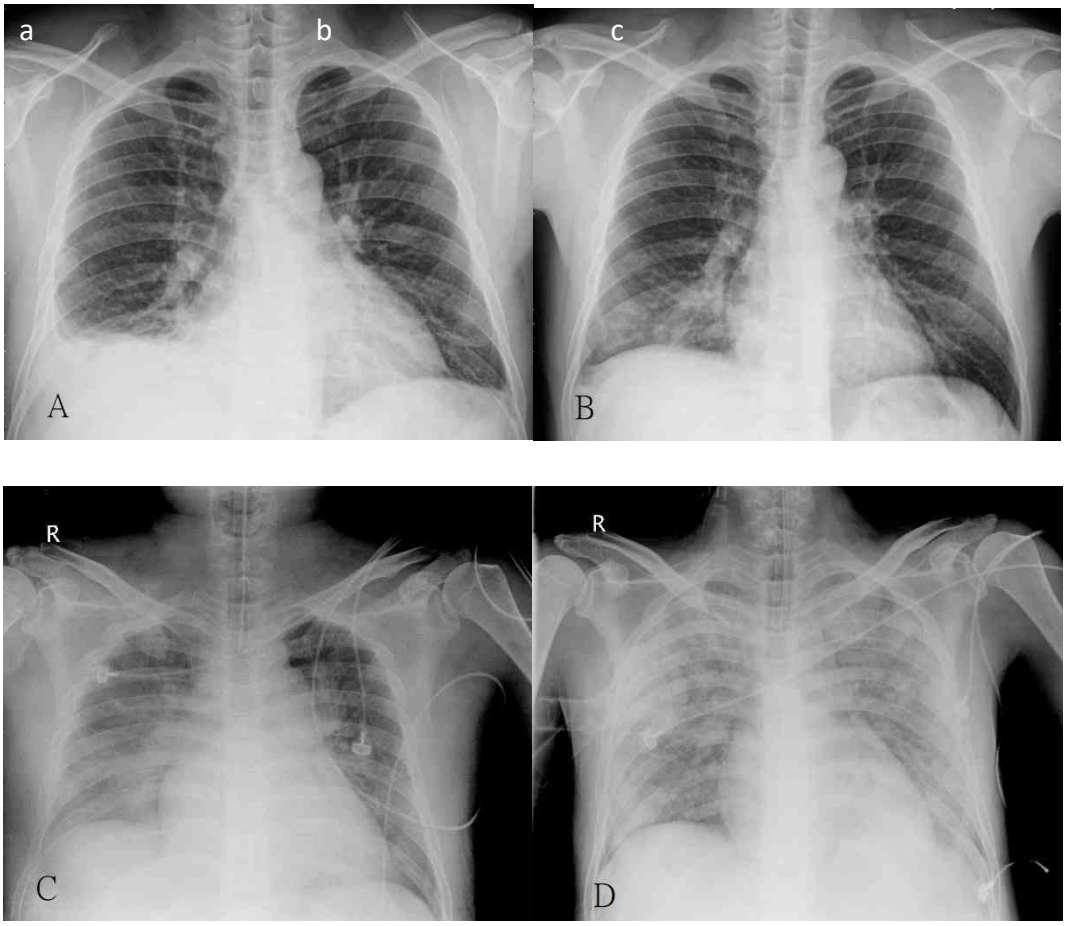

Figure 1. A. The chest X-ray from three years ago revealed blunting of the right costophrenic angle and increased infiltration in the right lower lung field. Right pneumonia with empyema was suspected. B. Two years ago, the chest X-ray revealed increased infiltration in the right lower lung field. Pneumonia was suspected at that time. C. Consolidation was noted in the bilateral hilar area, and acute lung edema was suspected. An endotracheal tube was also inserted for acute respiratory failure. D. Diffuse infiltration was noted in the bilateral lung fields, and peripheral lung involvement was predominant. Acute respiratory distress syndrome was suspected.

Fatal Case of Alcoholic Liver Cirrhosis Complicated by Tuberculosis Bacteremia: A Case Report

酒精性肝硬化併發結核菌血症致死病例報告

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中文摘要

本文報告一例 36 歲男性酒精性肝病患者，因發燒及右上肢腫脹入院。住院期間，患者被診斷為肝硬化併發開放性肺結核、鮑氏不動桿菌感染和結核菌血症。儘管給予包括抗結核藥物和支持性治療等積極治療，患者最終仍因多重器官衰竭死亡。本病例突顯了肝硬化患者結核感染的診斷和治療挑戰，並強調了早期診斷和個人化治療方法的重要性。

關鍵字：酒精性肝硬化、肺結核菌血症、急性呼吸窘迫症候群

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Fu-Jen Journal of Medicine

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