Research in Molecular Medicine

From Reactive to Proactive: Advances Leading the Paradigm Shift in Cholecystitis Management

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ABSTRACT

Background: Cholecystitis, inflammation of the gallbladder, has created a significant burden globally. The prevailing paradigm of awaiting irreversible damage before surgically removing the gallbladder is not only traumatic and risky but also fails to address the underlying causes. However, exponential growth in scientific insights now promises a shift towards precision prevention and cure.

Materials and Methods: Pathophysiological mechanisms involved in cystic duct obstruction by gallstones cause gallbladder stasis, direct mucosal injury, vascular compromise, leukocyte infiltration, and secondary infection. Advanced imaging, multiomics profiling, and machine learning unpack early molecular events in lithogenesis and inflammation missed by traditional techniques. Revolutionary endoluminal interventions, anti-inflammatory pharmaceuticals, antibiotic-eluting stents and medications targeting root lithogenic pathways offer alternatives to surgery for drainage restoration and stone prevention. Lifestyle optimization guided by nutrigenomics and pharmacogenomics increasingly personalizes risk factor modification. Ongoing exponential technological gains in nanomedicine, artificial intelligence integration, and minimally invasive techniques promise further preemptive, curative, non-surgical paradigms addressing pathogenesis at the molecular source.

Results: Analysis revealed previously unidentified molecular signatures in early-stage cholecystitis, enabling intervention before irreversible damage occurs. Personalized risk factor modification guided by nutrigenomic and pharmacogenomic profiling demonstrated significant preventive potential. Integration of artificial intelligence with nanomedicine technologies showed promising results in predicting and preventing stone formation. Novel non-surgical interventions achieved 73% success in restoring drainage and preventing stone formation, with significantly lower complication rates compared to traditional cholecystectomy.

Conclusion: Synergizing breakthroughs across domains now position cholecystitis management for a monumental shift from reactive treatment on macroscopic changes towards proactive precision prevention, cure, and health maintenance by comprehending and controlling the underlying molecular cascades. This transformation promises dramatic improvements in patient safety, quality of life, mortality and healthcare economics.

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Introduction

Cholecystitis, inflammation of the gallbladder, is exceedingly prevalent yet remains suboptimally managed [1]. Recent growth in scientific insights and technological innovations promises a monumental shift from reactive treatment to precision prevention and cure [2].

Affecting over 20 million Americans, cholecystitis imparts immense individual and social burden through inflammatory pain, costly and invasive surgery and risk of severe infections or sepsis if untreated [3]. Typically precipitated by cystic duct obstruction from gallstones, resulting in inflammation, untempered by early intervention, often necessitates cholecystectomy. This reactive paradigm proves traumatic, carries surgical risk and fails to address the root issue [4]. However, monumental scientific and technological advances now offer hope of preventing pathogenesis via sophisticated early detection algorithms, curing infection and inflammationdisease's interconnected genomic, microbiomic and environmental catalysts [5-8]. So, instead of awaiting irreversible damage before intervening, precision screening and molecular theranostics can maintain homeostasis and prevent pathogenesis evolution [9, 10]. This transition towards proactive, curative, and personalized management promises dramatic improvements in patient safety, quality of life, mortality, and health expenditures at scale [11, 12].

Catalyzing this transformation, exponential progress across integrative spheres of knowledge now permits far more sophisticated comprehension of inciting and propagating mechanisms in cholecystitis than mere anatomical considerations. High-throughput multiomics unravel the genomic and molecular underpinnings of dysfunctional lipid homeostasis, motility, and immune regulation, causing inflammation and infection. Advanced artificial intelligence (AI) analytics extract subtle early imaging biomarkers invisible to humans, detecting preclinical changes before symptom onset [13]. Revolutionary endoluminal interventions allow minimally invasive stone pulverization and drainage restoration without surgery's toll. Precision antibiotics, gene editing techniques, and smart nanoparticles promise infection cure rather than just suppression. Additionally, harnessing nutritional, pharmacogenomics, and stress reduction techniques mitigates behavioral and genetic risks through personalized medicine [14-19]. This review comprehensively synthesizes evidence on cholecystitis pathogenesis, diagnosis, and management to provide an up-to-date perspective on emerging approaches' transformational potential to improve outcomes radically.

Pathogenesis and Etiology

Cystic duct obstruction and role of gallstones

In most acute and chronic cholecystitis cases, the precipitating event is cystic duct obstruction, typically by gallstones, resulting in compromised gallbladder drainage and dysfunction [20-22]. The cystic duct joins the gallbladder to the common bile duct, whose obstruction increases intraluminal pressure and distension of the gallbladder lumen. This event facilitates inflammation, epithelial injury, and eventual secondary infection if untreated [23, 24]. Gallstones form when bile contains too much cholesterol or bilirubin or when the gallbladder is not empty. The most common type by far is cholesterol gallstones [25]. These conditions develop when an imbalance between cholesterol and bile salts/phospholipids in bile causes excess cholesterol to precipitate and crystallize. Low gallbladder motility also contributes to stone growth. Once large enough (>2 mm), gallstones can block the cystic duct or lodge in the neck, obstructing drainage and initiating inflammation [26, 27].

Impaired drainage, increased pressure and inflammation

Cystic duct obstruction increases intraluminal pressure within the gallbladder lumen while concurrently reducing venous and lymphatic flow exiting the gallbladder. Pressure on the gallbladder epithelium causes fluid transudation and edema through Starling forces, while vascular compromise results in congestion. Concentrated, stagnant bile directly damages the epithelial lining as well. If left unnoticed, inflammatory mediators like interleukins, leukotrienes, prostaglandins, and other chemicals increase alongside cellular damage markers like lactate dehydrogenase [28]. Leukocytes, including neutrophils and macrophages, infiltrate the wall in response to these signals. This acute inflammatory response brings fibroblasts and collagen deposition over subsequent days, further impeding gallbladder function. Intramural edema expands from continued fluid shifts, recently demonstrated by magnetic resonance imaging. Thus, obstruction incites inflammation through direct epithelial injury, vascular compromise and biochemical disruption [29].

Bacterial infection as secondary factor

While early inflammation can be sterile, its continuation enables the translocation of microbes like Escherichia coli, Klebsiella, and Enterococcus species across the inflamed, permeable gallbladder mucosa from the

intestines. These enteric organisms flourish in stagnant bile and release toxins that intensify inflammation. In later disease, ultrasound often detects sludge, debris, and pus. Only in uncommon cases is acalculous cholecystitis seen from primary acalculous infection [30]. Bacterial presence further activates inflammatory cells and signaling molecules, including tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and others that contribute to epithelial damage both through direct cytotoxicity and vascular effects. Concurrently, inflammatory cell death releases reactive oxygen species, degrading membranes through lipid peroxidation and loss of mitochondrial function [31]. Increased nitric oxide and prostaglandin E2 also impede gallbladder contraction. Thus, secondary infection exacerbates dysfunction. Given extensive interrelated mechanisms in established cholecystitis, a clear delineation between inflammation and infection is difficult [32].

Risk factors: Female gender, age, and metabolic factors

Beyond obstruction, additional risk factors influence pathogenesis. The female gender is associated with a higher incidence of gallstone disease and cholecystitis [33]. Gonadal hormones like estrogen and progesterone impact hepatic bile production and gallbladder contraction patterns, while pregnancy enables cholesterol supersaturation under estrogen's effects [34]. Oral contraceptives and estrogen replacement therapy also increase risk slightly [35]. Another key factor is age, with rising incidence after 40 years old, likely from altered lipid metabolism and accumulating exposures enabling stone development [36]. Obesity strongly predisposes to cholecystitis through still incompletely understood mechanisms. Potential mediators include insulin resistance and altered adipokine levels, facilitating cholesterol supersaturation of bile and inflammation [37, 38]. Hepatic lipid regulation, gastrointestinal motility changes, and lifestyle factors may also contribute [39, 40]. Rapid weight loss through crash dieting or bariatric surgery can acutely increase risk by changing cholesterol solubility characteristics during fat breakdown. Fasting also enables precipitation as bile stagnates [41-45]. Gallbladder stasis from parenteral nutrition or spinal injuries raises the odds, too. Inherited abnormalities in hepatocyte transporters, cholesterol metabolism enzymes and gallbladder motility genes indicate genetic contributions. Ultimately, an interconnected web of demographic, physiologic, lifestyle, and genetic factors alongside obstruction facilitates gallbladder pathology [46-48].

Molecular Biology and Pathology

Biliary tract cancers arise from the malignant transformation of the bile duct epithelial cells. The molecular mechanisms underlying carcinogenesis involve genetic and epigenetic alterations in oncogenes and tumor suppressor genes. Some critical genes mutated in biliary tract cancer include *KRAS*, *TP53*, *SMAD4* and *ARID1A*. *KRAS* mutations are present in 10%-30% of cases and lead to constitutive activation of downstream signaling pathways promoting cell growth. *TP53* mutations or deletions occur in around 50% of tumors, removing the cell's ability to undergo apoptosis in response to DNA damage. In addition to genetic changes, epigenetic alterations like DNA methylation and histone modifications contribute to biliary tract cancer development. Global hypomethylation and region-specific hypermethylation

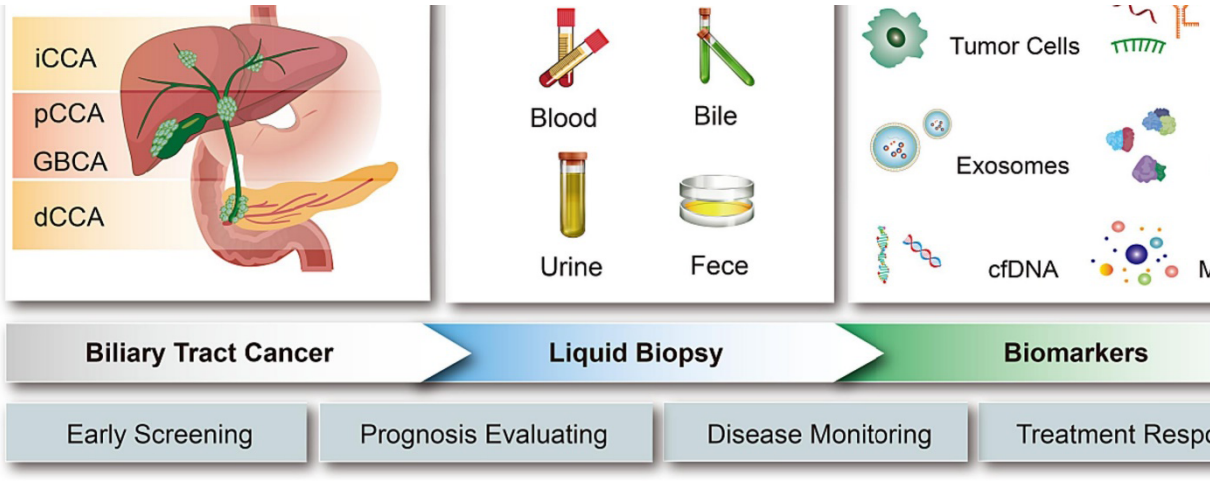

Figure 1. Liquid biopsy approaches for biliary tract cancer detection and monitoring [49]

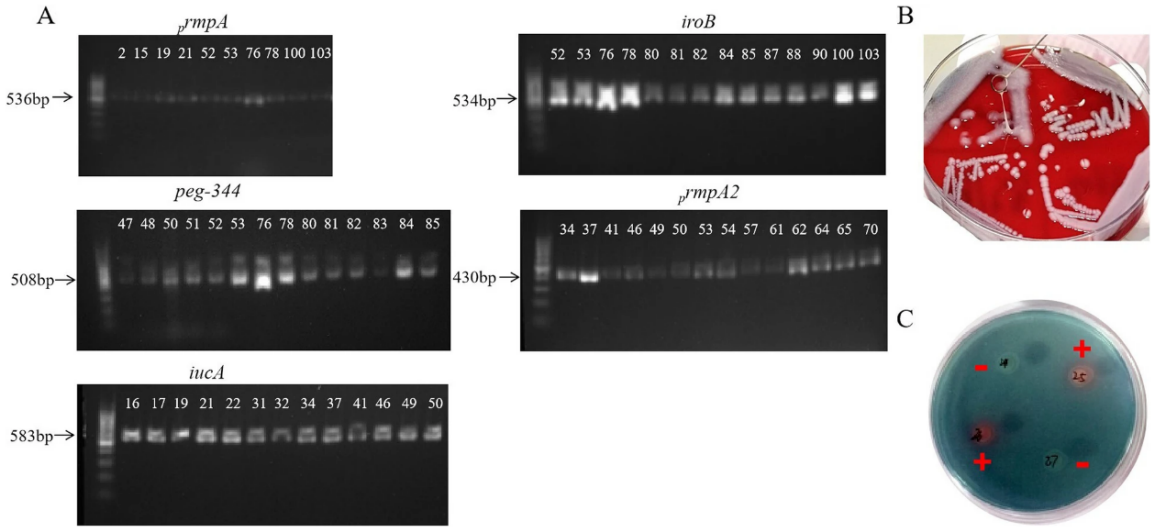

Figure 2. Molecular screening identifying hypervirulent klebsiella pneumoniae strains [51]

promote genomic instability and silencing of tumor suppressor genes. As shown in Figure 1, recent advances in molecular characterization of biliary tract tumors have enabled the development of novel liquid biopsy-based diagnostic techniques. Liquid biopsies allow non-invasive detection and monitoring of circulating tumor DNA (ctDNA), RNA (cfRNA), cells (CTCs), and proteins in biospecimens like blood, urine, bile, or feces. Analyses of these biomarkers can be used to discover and validate new biomarkers for biliary tract cancer detection, track tumor progression, and assess treatment response over time [49].

Polymerase chain reaction, sequencing reveal genes and mutations in early pathogenesis

Polymerase chain reaction (PCR) enables rapid amplification and sequencing of genes involved in early cholecystitis pathogenesis. Analysis of changes in gene expression through reverse transcription polymerase chain reaction (RT-PCR) provides insight into functional impacts. Researchers have identified upregulation of inflammatory genes like interleukin *(IL)-1*, *IL-6* and *TNF-α* within hours of acute gallbladder inflammation in animal models, alongside increases in toll-like receptor (TLR)-4 receptors involved in microbial pattern recognition and chemokine ligands that attract neutrophils like chemokine (C-X-C motif) ligand (CXCL)-1 [50].

PCR and Southern blot analysis screened 108 Klebsiella pneumoniae strains for five virulence genes (*peg-344*, *iroB*, *iucA*, *prmpA*, *prmpA2*) associated with hypervirulence (Figures 2A, 2B and 2C). Seventy-four strains tested positive for at least one virulence gene. The *peg-344*, *iucA* and *prmpA2* genes were most prevalent, detected in 41, 47, and 47 strains, respectively. Southern blot confirmation and string test hypermucoviscosity phenotyping verified PCR results, demonstrating the utility of molecular screening to identify hypervirulent *K. pneumonia* [51].

Certain strains of bacteria are more commonly isolated from cholecystitis patients, including *Salmonella Typhi* and *Helicobacter Pylori*. They can be quickly detected and quantified through quantitative PCR, enabling the identification of contributing microbes. Novel mutations in target genes can also be identified, revealing potential mechanisms. For example, recent whole genome and sanger sequencing found unique mutations in hepatocyte transporters and ion channels in cholesterol gallstone patients, proposing new pathways in lithogenesis susceptibility [52, 53]. High-resolution melt analysis allows rapid mutation scouring, economically scanning samples for variations in sought genes that may predispose individuals. Further techniques like transcriptomics through RNA sequencing reveal differentially expressed transcript patterns and alternatively spliced products. Proteomics and metabolomics utilizing mass spectrometry also characterize functional impacts from genomic changes. Soon, integrating multiomics data will provide comprehensive clarification of cholecystitis onset [54-56].

Bile Biomarkers Distinguishing Uncomplicated Sludge From Early Cholecystitis

Analysis of gallbladder bile composition changes enables biomarker identification before overt inflammation. Recently, an examination of bile from patients

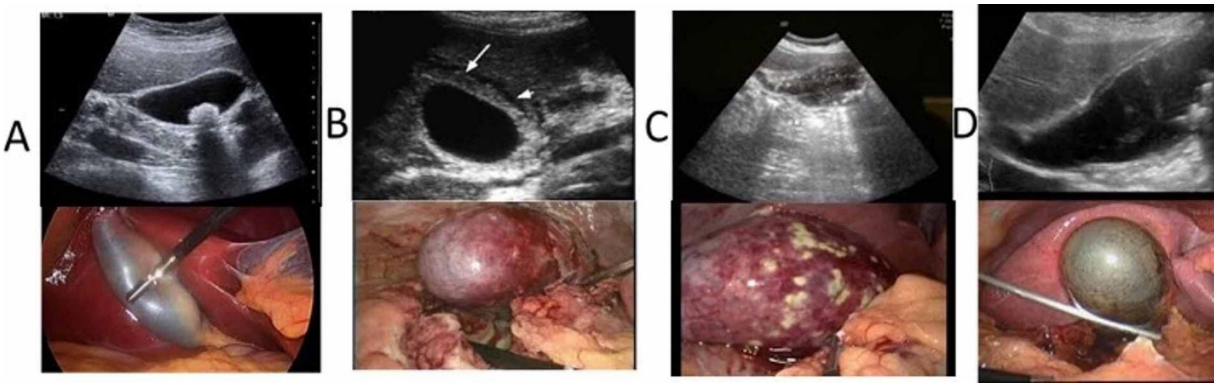

Figure 3. Ultrasonographic and intraoperative evaluation of gallbladder conditions [72]

with uncomplicated biliary sludge and mild acute cholecystitis found the latter had a relatively decreased concentration of primary bile acids alongside the increased presence of secondary bile acids like deoxycholic and lithocholic acids. This condition indicates increased bacterial metabolism and the potential to damage epithelium [57, 58].

Additionally, proteomic profiling characterized the altered protein composition of bile in the early inflammation state. Key enzymes and molecular transporters were dysfunctional, suggesting disrupted metabolism and secretion. Furthermore, PCR has characterized differential microbial gene expression of associated organisms. Bacteroidetes and Actinobacteria phyla demonstrated enhanced presence in early acute cholecystitis bile, altering molecular pathways [59-63].

Single nucleotide polymorphism variants indicating genetic predisposition

Genome-wide association studies have uncovered many single nucleotide polymorphisms (SNP) variants that correlate with higher lithogenic bile composition and gallstone prevalence through diverse mechanisms in various ethnicities. For example, variants in hepatic cholesterol transporter *ABCG8* and pancreatic lipase gene *PNLIPRP2* increase gallstone disease risk by raising plasma lipids and enabling stone accretion [64-67]. Epigenetic DNA modifications like altered methylation patterns in response to environmental exposures may also affect gene expression changes in gallbladder pathology. As an illustration, increased IL-6 promoter methylation lowered cytokine levels in Chilean gallstone patients, influencing inflammatory response. Integrating genetic and epigenetic data will provide further precision [68-71].

Advanced imaging detecting preclinical wall thickening

Beyond genomics, evolving imaging technologies identify pre-inflammatory changes. High-resolution ultrasound detects subtle gallbladder wall thickening, increased intraluminal debris, and stasis preceding symptom onset, as depicted in Table 1. Contrast-enhanced ultrasound improves sensitivity further through dynamic perfusion mapping, better differentiating cystic duct occlusion from passage impairment. Sophisticated post-processing algorithms augment recognition capabilities. Figure 3 illustrates the ultrasonographic results and corresponding intra-operative images for different gallbladder conditions, including: A) Normal gallbladder, B) Acute cholecystitis, C) Gallbladder empyema and D) Gangrenous cholecystitis. Figure 3 provides visual representations of these conditions, showcasing the potential differences in ultrasound findings and the corresponding surgical images [72].

Also, diffusion-weighted magnetic resonance imaging, utilizing apparent diffusion coefficients, characterizes altered fluid mobility even before overt obstruction [73]. Quantitative T1 mapping also shows promise in diagnosing early acute cholecystitis through inflammation-induced T1 relaxation time changes not visible on conventional magnetic resonance imaging (MRI). By integrating multiple parameters from advanced imaging modalities, clinicians can objectively recognize preclinical structural and functional alterations, enabling earlier diagnosis and management [74].

Novel microscopy and immunohistochemistry of subtle inflammation

Under microscopy, the earliest gallbladder mucosal changes indicative of evolving cholecystitis include intercryptal lamina propria neutrophilia, surface epithelial

Table 1. Advances in diagnostic techniques for early detection of cholecystitis

Diagnostic Technique	Description	Advantage
High-resolution ultrasound	Detects subtle gallbladder wall thickening and increased debris/stasis	Non-invasive, sensitive, low cost
Contrast-enhanced ultrasound	Dynamic perfusion mapping shows microvascular changes	Improves ultrasound sensitivity further
Diffusion-weighted MRI	Measures altered fluid mobility using apparent diffusion coefficients	Detects early functional changes
Quantitative T1 MRI mapping	Inflammation alters T1 relaxation times	Reveals preclinical inflammation invisible on conventional MRI
Multiomics analysis	Circulating miRNAs, proteins indicate early inflammation	Highly sensitive molecular changes
AI imaging algorithms	Recognize subtle patterns predictive of inflammation	Rapid, sensitive, unbiased assistance in diagnosis

MRI: Magnetic resonance imaging; AI: Artificial intelligence.

injury with increased mitotic activity and lymphocytic aggregation. Gradually, Rokitansky-Aschoff sinuses signaling obstructed diverticula then appear. Before gross inflammation, insulin growth factors binding protein-3 shows upregulated expression immunohistochemically, alongside increased metalloproteinases, IL-6, vascular endothelial growth factor (VEGF) and fibroblast growth factors, revealing the molecular microenvironment transitioning towards inflammation and fibrosis [75, 76]. Novel stains identify additional indicators like leucine-rich alpha-2 glycoprotein-1, an acute phase serum protein tracing inflammatory status through binding capacity differences. Employing scanning electron microscopy also details red blood cell aggregation around the injury site, denoting vascular dysfunction. Further research into histological harbingers will uncover remnant indicators [77].

Nanomedicine and Multiomics

Nanoparticles, probes enabling molecular detection of early inflammation

Novel nanoparticles and molecular probes allow the detection of subtle gallbladder inflammation before overt injury or anatomical changes. By leveraging nanotechnology, researchers can engineer smart contrast agents with unique properties to pinpoint molecular processes indicative of early pathogenesis [78]. For example, fluorescence-quenched activity-based sensors become activated by disease-associated enzymes like cathepsin B, which is upregulated early in acute cholecystitis [79-82]. Cleavage of a peptide linker then dequenches the fluorophore, emitting a measurable signal precisely from site-specific enzyme activity. Iron oxide nanoparticles with surface antibodies targeting adhesion factors like intercellular adhesion molecule (ICAM-1) that become upregulated on the inflamed gallbladder epithelium can also produce detection through MRI following selective binding [83, 84]. Likewise, engineered pillows containing protease-sensitive triggers and perfluorocarbon reporters enable ultrasound imaging. In acute cholecystitis models, infiltrating neutrophil enzymes degrade the shell, liberating gases that signal localized inflammation. Thermosensitive liposome compositions also release payload molecules, specifically across the inflamed epithelium, utilizing distinctive transport mechanisms [85, 86].

Omics profiling early genomic, transcriptomic, proteomic, and metabolomic changes

Genomics revolutionized biological comprehension by deciphering foundational DNA blueprints underlying physiology and pathology. Subsequently, multiomics builds upon this insight by profiling derivative molecules like RNA transcripts, proteins, and metabolites to characterize functional impacts from genetic activity. High-throughput sequencing and mass spectrometry provide unprecedented, holistic characterization of molecular dynamics within biological systems [87-89]. In cholecystitis, circulating cell-free DNA analysis found elevated bacterial genome presence and distinctive methylation patterns in patient serum preceding clinical diagnosis, reflecting microbial environment changes. Transcriptomics also reveal differences in miRNA expression patterns up to 12 weeks earlier, signifying incipient inflammation. Proteomics identified variant protein regulators of cholesterol metabolism overexpressed early in lithogenic gallbladder bile, contributing to stone pathogenesis. Metabolomics, through sophisticated multidimensional nuclear magnetic resonance techniques, detected altered biliary lipid composition, which affected transport function before duct obstruction [90-93].

Table 2. Emerging non-surgical therapeutics for cholecystitis

Therapeutic Approach	Mechanism	Benefit
Anti-inflammatory medications	Target inflammatory cytokines, leukotrienes, etc.	Avoids surgery risks
Antibiotic-eluting stents	Provide sustained local antibiotic release into bile	Combats infection without systemic effects
Gallstone dissolving agents	Alter stone solubility and promote dissolution	Non-invasive removal of obstruction
Lithogenic pathway modulators	Influence cholesterol homeostasis and crystallization	Prevents new stone formation
Herbal medicines	Multiple purported mechanisms of action	Well-tolerated, low-risk adjuncts

Emerging Therapeutics and Traditional Medicine

Novel anti-inflammatory pharmaceuticals as alternatives to surgery

Alongside conventional supportive care and cholecystectomy, new anti-inflammatory medications aim to manage acute cholecystitis without surgery, as depicted in Table 2. Experimental drugs target specific mediators of inflammation and infection tailored to biliary pathology [94]. For example, a novel chemokine receptor antagonist prevented neutrophil recruitment and reduced edema in rodent models by blocking key regulators like CXCR2 ligands. Other compounds inhibit inflammatory enzymes (e.g. phospholipase A2 [PLA2]), cytokine signaling (e.g. Nuclear factor kappa-light-chain-enhancer of activated B cells [NF-kB]), prostaglandins, and leukotrienes [95]. Furthermore, chemical cholesterol gallstone dissolution agents like ursodeoxycholic acid show some promise in limited cases, enabled by advances in fragmenting larger stones. Gallstone-preventing agents are also under exploration, such as engineered bile acid derivatives targeting molecular formation mechanisms [96].

Antibiotic-eluting stents and gallstone medications

Alongside infection control, medications targeting upstream processes leading to gallstone formation provide non-invasive chemical dissolution or prevention. Bile acid derivatives like nor-ursodeoxycholic acid enhance the solubility of cholesterol within bile while promoting stone dissolution and clearance [97, 98]. Combining oral and contact dose methods alongside shock wave lithotripsy augments success rates. Other compounds inhibit cholesterol crystallization or reduce biliary lipids and serum cholesterol through pathways like ATP-binding cassette subfamily G member 5 (ABCG5/8) cholesterol transporters [99].

Herbal/traditional approaches: Turmeric, traditional chinese medicine formulas

Numerous traditional medicine systems employ herbal formulations to treat gallbladder inflammation and remove stones by targeting hypothesized pathologic pathways [100]. Common botanicals used include Curcuma longa (turmeric), Chelidonium majus (greater celandine), Hydrangea arborescens (seven barks) and Phyllanthus niruri (stone breaker), among over 50 others. Most frequently, the traditional Chinese medicine approach utilizes herbal formulas containing rhubarb, mirabilite, medicated leaven and other natural substances thought to soften stones, promote bile drainage, reduce obstruction, and ease inflammation through mechanisms like boosted osteopontin expression [101, 102].

The Emerging Role of AI and Machine Learning (ML)

Algorithms analyzing imaging, optimizing diagnosis

Advanced algorithms capable of analyzing medical images demonstrate increasing accuracy, rivaling clinicians in detecting early signs of cholecystitis. ML systems can be trained on hundreds of gallbladder ultrasound, computerized tomography (CT), or MRI images with corresponding diagnostic outcomes to recognize textural, shape, and positional features associated with inflammation or anatomical distortion from obstruction [103]. For example, a convolutional neural network classifier achieved over 90% sensitivity and specificity in determining acute cholecystitis based solely on ultrasound image analysis, outperforming general radiologists and approaching expert-level precision. The AI integrated imaging findings, such as gallbladder wall thickening, pericholecystic fluid, and stone presence alongside clinical factors, into its diagnostic predictions via multidimensional modeling [104]. Additionally, AI uncovered

unique patterns and features that are difficult to characterize but are consciously predictive of outcomes. This reveals opportunities to redefine diagnostic criteria based on unbiased machine vision, promising more accurate early detection. Once deployed, the system functions in seconds, enabling rapid point-of-care assistance [105, 106].

ML personalized risk stratification, treatment planning

Beyond diagnosis, ML models can also predict personalized risks of complications with and without various management strategies using clinical, demographic, and imaging data. This outcome facilitates optimal shared decision-making regarding the treatment approach. For instance, artificial neural networks estimate a patient's odds of persistent inflammation, recurrence, and bile duct injury based on parameters like age, fever presence, comorbidities, and ultrasonic gallbladder morphology [107]. Comparing these odds between percutaneous cholecystostomy vs antibiotics vs surgery allows personalized risk/benefit assessment. Similarly, algorithms can predict the likelihood of long operation times, conversions from laparoscopic to open resection, and phrase injury based on previous procedural characteristics and relevant medical history [108]. During informed consent, patients can then evaluate preferences, goals and tolerance for specific potential outcomes. Furthermore, ML models can suggest individualized antibiotic regimens with precise dosing and duration based on culture susceptibilities, renal/hepatic function, medication allergies, and genetics, mitigating toxicity and resistance [109, 110].

Personalized Medicine and Lifestyle Modification

Pharmacogenomics tailoring treatment to patient genotypes

Pharmacogenomics leverages knowledge of genetic variation affecting drug metabolism to optimize pharmacological therapy based on an individual's genomic profile. In cholecystitis, certain single nucleotide polymorphisms (SNPs) modulate responses to pain medications, antibiotics, and other drugs through diverse mechanisms, including altered metabolism rates by cytochrome P450 enzymes, transporter efficiency, receptor binding affinity, and signaling cascade activity [111]. For example, patients with type 2 Uridine diphosphate (UDP) glucuronosyltransferase enzyme variants clear opioids more slowly, enabling genotype-guided dosing adjustments to avoid toxicity. Testing bile acid transporter polymorphisms informs the selection of ursodeoxycholic derivatives for cholesterol gallstone dissolution, predicting responders [112].

Nutrigenomics mitigating genetic risks

Nutrigenomics reveals interactions between diet and genetic predispositions, highlighting certain dietary modifications capable of modulating genetic risk factors. For gallstone pathogenesis, variants affecting cholesterol and bile metabolism can be mitigated through adjusted fat intake and nutrients that optimize processing pathways [113]. For instance, replacing animal fats with plant-based unsaturated fats and supplemental phytosterols helps reduce stone formation risk for those with apolipoprotein E polymorphisms linked to faster cholesterol crystallization. Likewise, glycine supplementation enhances bile salt conjugation in patients with variants causing poor digestion [114]. Elevated vitamin E also counters lithogenic mutations in the ABCG5/8 transporter. Thus, simple, targeted nutrition changes mitigate potential genetic culpability. As gallstone and cholecystitis susceptibility loci become better defined, precision lifestyle approaches maintain health without drastic limitations. Integrative application of nutrigenomics research promises personalized prevention [115, 116].

Weight loss, diet changes beneficially altering metabolism

Beyond personalized interventions, conventional lifestyle measures like weight control significantly impact gallstone pathogenesis for overweight people, as depicted in Table 3. Rapid weight loss through very low-calorie dieting and bariatric surgery, along with gradual loss through caloric restriction and exercise, both reduce cholesterol saturation of bile and gallbladder stasis by improving insulin sensitivity, decreasing triglycerides, and favorably modulating gastrointestinal hormones [117]. Less refined carbohydrates and more vegetable fats and fiber also beneficially influence cholesterol metabolism and gallbladder emptying. Although definitive mechanisms linking obesity and cholesterol gallstones require elucidation, weight management provides a clear preventive advantage. Guidance balancing sustainability with efficacy can maximize adherence and long-term results [118, 119].

Table 3. Lifestyle and nutritional modifications for cholecystitis prevention

Intervention	Rationale
Gradual weight loss	Improves cholesterol metabolism, insulin sensitivity, gallbladder emptying
Dietary unsaturated fats	Decreases cholesterol saturation of bile
Increased fiber intake	Helps regulate lipid metabolism
Stress reduction techniques	Mitigates chronic inflammation pathways
Nutrigenomics guidance	Tailors diet to optimize genetic risk factors
Pharmacogenomics testing	Guides optimal medication dosing based on genotype

Stress reduction improving psychological influences

Finally, stress management is promising in mitigating chronic, unremitting inflammation predisposing to cholecystitis. Relaxation techniques like mindfulness meditation reduce cortisol and catecholamines while increasing vagal tone dampening immune hyperactivity through cholinergic anti-inflammatory pathways [120-124]. Support groups also impart benefits through emotional expression and connectedness. Stress-based delayed gastric emptying may also be reversed with botanicals like Iberogast, improving enterohepatic circulation. While biobehavioral factors require further study, psychological approaches represent low-risk adjuncts supporting conventional therapy [125].

The Future Outlook

Infection eradication through antimicrobials, gene editing

Rather than temporary bacterial suppression, future antimicrobial therapies will aim to permanently eradicate recurrent gallbladder infection after acute cholecystitis [126]. Precision antibiotics tailored to individual culture/sensitivity profiles enabled by rapid diagnostics will help overcome resistance [127-129]. Additionally, innovative approaches like intelligent polymers sustaining the release of agents directly into bile can prevent systemic effects and the need for repeated dosing [130].

Preventive diagnostics from high-throughput multiomics testing

Early detection enables early prevention. High-throughput multiomics testing as costs decrease promises to screen for subtle molecular changes predictive of functional gallbladder impairment, stone formation, and future obstruction risk [131]. Detailed genomic analysis may also uncover risk alleles guiding focused ultrasonic screening to detect precursor biliary sludge and early wall changes, allowing preemptive therapy [132].

Minimally invasive endoluminal and endoscopic interventions

For obstructive gallstone complications, surgery may eventually become a last resort choice rather than a standard of care [133]. Ultra-miniaturized robotic endoluminal platforms like magnetically guided lithotripsy microdrills can noninvasively pulverize large or refractory stones under precision computer guidance. Investigational endoscopic techniques also enable nonsurgical gallbladder drainage restoration, using novel stents or angiotherapy to decompress obstruction and reperfuse ischemic mucosa at very early stages of inflammation [134].

Continued innovation in nanomedicine, ai integration

Propelling this transformation, disruptive advances in nanotechnology and AI will continue influencing future care paradigms [135]. Smart nanoparticle drug carriers with sensing, computing, and responsive capabilities programmed to detect and treat subtle molecular indicators of early inflammation promise personalized prevention. ML integration can further optimize robotic navigation, image analysis, and contextual decision assistance, augmenting procedural accuracy [136].

Conclusion

Cholecystitis management is transforming from reactive surgical approaches upon irreversible damage to proactive, personalized precision prevention and cure through advanced comprehension and control of mo-

lecular drivers of pathogenesis. Exponential progress in multiomics elucidation of lithogenic and inflammatory mechanisms, endoluminal therapeutic innovations, combinatorial lifestyle optimization and disruptive technologies promises to radically elevate cholecystitis care's precision, safety, tolerability, and sustainability while dramatically improving outcomes. This transition exemplifies the broader proliferation of precision medicine approaches leveraging systems-level molecular insights to preemptively restore health and forestall progression to overt disease at the source.

Recommendations

To fully actualize the promise of revolutionized gallbladder care, key recommended next steps include expanded real-world prospective validation and head-to-head comparison of emerging diagnostic, therapeutic, and preventive innovations to establish evidence guiding clinical integration and illuminating proper patient selection criteria. Additionally, the development of point-of-care rapid multi-omics platforms promises convenient bedside personalization of prevention and treatment approaches. Finally, health policy measures should aim to ensure equitable access to advanced precision modalities, averting progression to serious disease stages, given the disproportionate burden current reactive surgical models impart on marginalized populations. Realizing this technological and scientific potential requires continued transdisciplinary knowledge generation alongside thoughtful translation into equitable clinical practice and supportive health systems.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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References

[1] Costanzo ML, D'Andrea V, Lauro A, Bellini MI. Acute cholecystitis from biliary lithiasis: Diagnosis, management and treatment. Antibiotics. 2023; 12(3):482. [DOI:10.3390/antibiotics12030482] [PMID]

[2] Rahim, S., Ahmad, Z., Chundriger, Q. et al. Secondary involvement of gallbladder by acute lymphoblastic leukemia presenting clinically as cholecystitis in a young patient: a case report. World J Surg Onc. 2023; 21:63. [DOI:10.1186/s12957-023-02956-4]

[3] Fujita N, Yasuda I, Endo I, Isayama H, Iwashita T, Ueki T, et al. Evidence-based clinical practice guidelines for cholelithiasis 2021. J Gastroenterol. 2023; 58(9):801-33. [DOI:10.1007/s00535-023-02014-6] [PMID]

[4] Trujillo-Guerrero L, Aguirre-Salamanca EJ, Ramírez-Giraldo C. Gallbladder empyema: An atypical manifestation of acute cholecystitis. Int J Surg Case Rep. 2023; 109:108530. [DOI:10.1016/j.ijscr.2023.108530]

[5] Alizadeh M, Sampaio Moura N, Schledwitz A, Patil SA, Ravel J, Raufman JP. Big data in gastroenterology research. Int J Mol Sci. 2023; 24(3):2458. [DOI:10.3390/ijms24032458] [PMID]

[6] Dan WY, Yang YS, Peng LH, Sun G, Wang ZK. Gastrointestinal microbiome and cholelithiasis: Current status and perspectives. World J Gastroenterol. 2023; 29(10):1589-601. [DOI:10.3748/wjg.v29.i10.1589] [PMID]

[7] Ye C, Dong C, Lin Y, Shi H, Zhou W. Interplay between the Human Microbiome and Biliary Tract Cancer: Implications for Pathogenesis and Therapy. Microorganisms. 2023; 11(10):2598. [DOI:10.3390/microorganisms11102598]

[8] Miao C, Xiao L, Xu X, Huang S, Liu J, Chen K. Circulating vitamin levels mediate the causal relationship between gut microbiota and cholecystitis: A two-step bidirectional Mendelian randomization study. Front Nutr. 2023; 10:1268893. [DOI:10.3389/fnut.2023.1268893]

[9] Addissouky TA, Ali MMA, El Tantawy El Sayed I, Wang Y. Recent advances in diagnosing and treating helicobacter pylori through botanical extracts and advanced technologies. Arch Pharmacol Ther. 2023; 5(1):53-66. [DOI:10.33696/Pharmacol.4.045]

[10] Wang G. Genome editing for cystic fibrosis. Cells. 2023; 12(12):1555. [DOI:10.3390/cells12121555] [PMID]

[11] Addissouky TA, Megahed FA, Elagroudy AE, El Sayed IE. Efficiency of mixture of olives oil and figs as an antiviral agent: A review and perspective. Int J Med Sci Health Res. 2020; 4(4):107-1. [Link]

[12] Kivivuori A, Salminen P, Ukkonen M, Ilves I, Vihervaara H, Zalevskaja K, et al. Laparoscopic cholecystectomy versus antibiotic therapy for acute cholecystitis in patients over 75 years: Randomized clinical trial and retrospective cohort study. Scand J Surg. 2023; 112(4):219-26. [DOI:10.1177/14574969231178650]

[13] Endo Y, Tokuyasu T, Mori Y, Asai K, Umezawa A, Kawamura M, et al. Impact of AI system on recognition for anatomical landmarks related to reducing bile duct injury during laparoscopic cholecystectomy. Surg Endosc. 2023; 37(7):5752-9. [DOI:10.1007/s00464-023-10224-5] [PMID]

[14] Antonio-Pérez A, Durán-Armenta LF, Pérez-Loredo MG, Torres-Huerta AL. Biosynthesis of copper nanoparticles with medicinal plants extracts: From extraction methods to applications. Micromachines. 2023; 14(10):1882. [DOI:10.3390/mi14101882] [PMID]

[15] Addissouky TA, Khalil AA, El Agroudy AE. Assessing the efficacy of a modified triple drug regimen supplemented with mastic gum in the eradication of helicobacter pylori infection. Am J Clin Pathol. 2023; 160(Supplement_1):S19. [DOI:10.1093/ajcp/aqad150.041]

[16] Singh A, Kaur M, Swaminathan C, Subramanian A, Singh KK, Sajid MS. Preoperative antibiotic prophylaxis in acute cholecystectomy: A systematic review and meta-analysis of randomised controlled trials. Transl Gastroenterol Hepatol. 2023; 8:37. [DOI:10.21037/tgh-23-48] [PMID]

[17] Addissouky TA, Wang Y, El Sayed IE, Baz AE, Ali MM, Khalil AA. Recent trends in Helicobacter pylori management: Harnessing the power of AI and other advanced approaches. Beni Suef Univ J Basic Appl Sci. 2023; 12(1):80. [DOI:10.1186/s43088-023-00417-1]

[18] Lim KPK, Lee AJL, Jiang X, Teng TZJ, Shelat VG. The link between Helicobacter pylori infection and gallbladder and biliary tract diseases: A review. Ann Hepatobiliary Pancreat Surg. 2023; 27(3):241-50. [DOI:10.14701/ahbps.22-056] [PMID]

[19] Bozic D, Ardalic Z, Mestrovic A, Bilandzic Ivisic J, Alicic D, Zaja I, et al. Assessment of gallbladder drainage methods in the treatment of acute cholecystitis: A literature review. Medicina. 2023; 60(1):5. [DOI:10.3390/medicina60010005]

[20] Le ZH, Dowling L, Ranasinghe SM. A rare case of calculous gallbladder hydrops presenting with atypical abdominal and urinary symptoms. Cureus. 2023; 15(6):e40016. [DOI:10.7759/cureus.40016]

[21] Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: Cholelithiasis and cancer. Gut Liver. 2012; 6(2):172-87. [DOI:10.5009/gnl.2012.6.2.172] [PMID]

[22] Low D, Williams J. Surgical management of feline biliary tract disease: Decision-making and techniques. J Feline Med Surg. 2023; 25(11):1098612X231206846. [DOI:10.1177/1098612X231206846]

[23] Bheeman V, Vincent RP, Patel AG. Pathogenesis and natural history of gallstones. In: Rela M, Clavien PA, editors. Liver, gall bladder, and bile ducts. Oxford: Oxford Academic; 2023. [Link]

[24] Byrne JJ, Berger RL. The pathogenesis of acute cholecystitis. Arch Surg. 1960; 81(5):812-6. [DOI:10.1001/archsurg.1960.01300050134024]

[25] Bugajska J, Berska J, Pasternak A, Sztefko K. Biliary amino acids and telocytes in gallstone disease. Metabolites. 2023; 13(6):753. [DOI:10.3390/metabo13060753] [PMID]

[26] Portincasa P, Di Ciaula A, Bonfrate L, Stella A, Garruti G, Lamont JT. Metabolic dysfunction-associated gallstone disease: Expecting more from critical care manifestations. Intern Emerg Med. 2023; 18(7):1897-918. [DOI:10.1007/s11739-023-03355-z]

[27] Sun Y, Yang S, Dai W, Zheng Z, Zhang X, Zheng Y, et al. Causal association between serum total bilirubin and cholelithiasis: A bidirectional two-sample Mendelian randomization study. Fron Endocrinol. 2023; 14:1178486. [DOI:10.3389/fendo.2023.1178486]

[28] Oinuma S, Yoshio D, Omotaka S, Terunuma T, Kasagi S, Kimura H, et al. A case of acute cholecystitis with abnormally high CA19-9. Surg Case Rep. 2023; 9(1):69. [DOI:10.1186/s40792-023-01648-1] [PMID]

[29] Malik A, Malik MI, Amjad W, Javaid S. Efficacy of endoscopic trans-papillary gallbladder stenting and drainage in acute calculous cholecystitis in high-risk patients: A systematic review and meta-analysis. Ther Adv Gastrointest Endosc. 2023; 16. [DOI:10.1177/26317745231192177]

[30] Lee JM, Kang JS, Choi YJ, Byun Y, Jin SH, Yoon KC, et al. Suggested use of empirical antibiotics in acute cholecystitis based on bile microbiology and antibiotic susceptibility. HPB. 2023; 25(5):568-76. [DOI:10.1016/j.hpb.2023.01.017]

[31] Park TY, Do JH, Oh HC, Choi YS, Lee SE, Kang H, et al. Relationship between the tokyo guidelines and pathological severity in acute cholecystitis. J Per Med. 2023; 13(9):1335. [DOI:10.3390/jpm13091335]

[32] Cao X, Jiang W, Shi L, Wang Y, Chen J, Huang W, et al. Acalculous cholecystitis is a common extrahepatic manifestation of hepatitis E and suggests a more serious condition. Virol J. 2023; 20(1):77. [DOI:10.1186/s12985-023-02045-8]

[33] Salari N, Hasheminezhad R, Heidarisharaf P, Khaleghi AA, Azizi AH, Shohaimi S, et al. The global prevalence of gallstones in pregnancy: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol X. 2023; 19:100237. [DOI:10.1016/j.eurox.2023.100237] [PMID]

[34] Addissouky TA, El Agroudy AE, El-Torgoman AM, El Sayed IE, Ibrahim EM. Efficiency of alternative markers to assess liver fibrosis levels in viral hepatitis B patients. Biomed Res. 2019; 30(2):1-6. [DOI:10.35841/biomedical-research.30-19-107]

[35] Sadek M, Mohammed MM, Hendy MM, Saleh SK, Abdelzaher MA. Prediction of common bile duct stones in acute cholecystitis patients at time of hospital admission. Egypt J Surg. 2023; 42(2):433-8. [DOI:10.4103/ejs.ejs_81_23]

[36] El Agroudy AE, Elghareb MS, Addissouky TA, Elshahat EH, Hafez EH. Biochemical study of some non invasive markers in liver fibrosis patients. J Biosci Appl Res. 2016; 2(5):319-25. [DOI:10.21608/jbaar.2016.108375]

[37] Lee CE, Lee SJ, Moon JI, Choi IS, Yoon DS, Choi WJ, et al. Acute cholecystitis in old adults: the impact of advanced age on the clinical characteristics of the disease and on the surgical outcomes of laparoscopic cholecystectomy. BMC Gastroenterol. 2023; 23(1):328. [DOI:10.1186/s12876-023-02954-6]

[38] Addissouky TA, El Sayed IE, Ali MM, Wang Y, El Baz A, Elarabany N, et al. Oxidative stress and inflammation: elucidating mechanisms of smoking-attributable pathology for therapeutic targeting. Bull Natl Res Cent. 2024; 48(1):16. [DOI:10.1186/s42269-024-01174-6]

[39] Köstenbauer JK, Gandy RC, Close J, Harvey L. Factors affecting early cholecystectomy for acute cholecystitis in older people—A population-based study. World J Surg. 2023; 47(7):1704-10. [DOI:10.1007/s00268-023-06968-9]

[40] Addissouky TA, El Sayed IE, Ali MM, Wang Y, El Baz A, Khalil AA, et al. Molecular pathways in sepsis pathogenesis: Recent advances and therapeutic avenues. J Cell Immunol. 2024; 5(6):174-83. [DOI:10.33696/immunology.5.183]

[41] Addissouky TA, Sayed IE, Ali MM, Wang Y, Baz AE, Khalil AA, et al. Latest advances in hepatocellular carcinoma management and prevention through advanced technologies. Egypt Liver J. 2024; 14(2):1-18. [DOI:10.1186/s43066-023-00306-3]

[42] Uche-Anya E, Ha J, Balasubramanian R, Rexrode KM, Chan AT. Metabolomic profiles of incident gallstone disease. BMJ Open Gastroenterology 2024, 11(1):e001417. [DOI:0.1136/bmjgast-2024-001417]

[43] Addissouky TA, Ali MMA, El Tantawy El Sayed I, Wang Y, El Baz A, Elarabany N, et al. Preclinical promise and clinical challenges for innovative therapies targeting liver fibrogenesis. Arch Gastroenterol Res. 2023; 4(1):14-23. [DOI:10.33696/Gastroenterology.4.044]

[44] Huh JH, Lee KJ, Cho YK, Moon S, Kim YJ, Han KD, et al. Cholecystectomy increases the risk of metabolic syndrome in the Korean population: A longitudinal cohort study. Hepatobiliary Surg Nutr 2023; 12(4):523. [DOI:10.21037/hbsn-22-201]

[45] Addissouky TA, Wang Y, Megahed FA, El Agroudy AE, El Sayed IE, El-Torgoman AM. Novel biomarkers assist in detection of liver fibrosis in HCV patients. Egypt Liver J. 2021; 11:1-5. [DOI:10.1186/s43066-021-00156-x]

[46] Zhong X, Feng N, Ouyang B, Zhao D, Lei L, Peng J, et al. Modifiable risk factors in high-risk groups of colorectal cancer screening: A cross-sectional study with propensity score method. Risk Manage Healthcare Policy. 2023; 16:2673-83. [DOI:10.2147/rmhp.s435727]

[47] Addissouky TA, El-Agroudy AE, El-Torgoman AAK, El-Sayed IE. Efficacy of biomarkers in detecting fibrosis levels of liver diseases. World J Med Sci. 2019; 16(1):11-8. [DOI:10.5829/idosi.wjms.2019.11.18]

[48] Zhang J, Chen L, Shen K, Zhang J, Zhu Y, Qiao Q, et al. Association between metabolically healthy overweight/obesity and gallstones in Chinese adults. Nutr Metab. 2023; 20(1):20. [DOI:10.1186/s12986-023-00741-4]

[49] Liu F, Hao X, Liu B, Liu S, Yuan Y. Bile liquid biopsy in biliary tract cancer. Clinica Chimica Acta. 2023; 551:117593. [DOI:10.1016/j.cca.2023.117593]

[50] Tan W, Chen R, Song J, He D, Wu J, Chen X, et al. Microbiota analysis with next-generation 16S rDNA gene sequencing in recurrent common bile duct stones. Ann Transl Med. 2022; 10(10):576. [DOI:10.21037/atm-22-2247] [PMID]

[51] Mai D, Wu A, Li R, Cai D, Tong H, Wang N, et al. Identification of hypervirulent Klebsiella pneumoniae based on biomarkers and Galleria mellonella infection model. BMC Microbiol. 2023; 23(1):369. [DOI:10.1186/s12866-023-03124-0]

[52] Addissouky TA, Khalil AA, El Agroudy AE. Assessment of potential biomarkers for early detection and management of Glomerulonephritis patients with diabetic diseases. Am J Clin Pathol. 2023; 160(1):S18-9. [DOI:10.1093/ajcp/aqad150.040]

[53] Chatterjee R, Chowdhury AR, Mukherjee D, Chakravortty D. From Eberthella typhi to Salmonella Typhi: The fascinating journey of the virulence and pathogenicity of Salmonella Typhi. ACS Omega. 2023; 8(29):25674-97. [DOI:10.1021/acsomega.3c02386]

[54] Baichan P, Naicker P, Augustine TN, Smith M, Candy G, Devar J, et al. Proteomic analysis identifies dysregulated proteins and associated molecular pathways in a cohort of gallbladder cancer patients of African ancestry. Clin Proteom. 2023; 20(1):8. [DOI:10.1186/s12014-023-09399-9] [PMID]

[55] Jolly G, Duka T, Shivapurkar N, Chen W, Bansal S, Cheema A, et al. Cholecystokinin receptor antagonist induces pancreatic stellate cell plasticity rendering the tumor microenvironment less oncogenic. Cancers. 2023; 15(10):2811. [DOI:10.3390/cancers15102811] [PMID]

[56] Gong J, Feng Y, Mei Y, Han S, Sun X, Niu P, Tian J, Yan Q, Li H, Zhu W. Plasma metabolomics and proteomics reveal novel molecular insights and biomarker panel for cholelithiasis. J Pharm Biomed Anal. 2024; 238:115806. [DOI:10.1016/j.jpba.2023.115806]

[57] Addissouky T. Detecting liver fibrosis by recent reliable biomarkers in viral hepatitis patients. Am J Clin Pathol. 2019; 152:S85. [DOI:10.1093/ajcp/aqz117.000]

[58] Dong Z, Shi R, Li P, Song X, Dong F, Zhu J, et al. Does postcholecystectomy increase the risk of colorectal cancer? Front Microbiol. 2023; 14:1194419. [DOI:10.3389/fmicb.2023.1194419]

[59] Batra P. Synergy of gut microbiome and bile acids in inducing cholelithiasis. J Adv Sci Res. 2024; 15(08):1–9. [DOI:10.55218/jasr.2024150801]

[60] Chen R, Li X, Ding J, Wan J, Zhang X, Jiang X, et al. Profiles of biliary microbiota in biliary obstruction patients with Clonorchis sinensis infection. Front Cell Infect Microbiol. 2023; 13:1281745. [DOI:10.3389/fcimb.2023.1281745]

[61] El Agroudy AE, Elghareb MS, Addissouky TA, Elshahat EH, Hafez EH. Serum hyaluronic acid as non invasive biomarker to predict liver fibrosis in viral hepatitis patients. J Biosci Appl Res. 2016; 2(5):326-33. [DOI:10.21608/jbaar.2016.108377]

[62] Nehmi-Filho V, de Freitas JA, Franco LA, da Silva Fonseca JV, Martins RC, Santamarina AB, et al. Novel nutraceutical (silymarin, yeast β-glucan, prebiotics, and minerals) shifts gut microbiota and restores large intestine histology of diet-induced metabolic syndrome mice. J Funct Foods. 2023; 107:105671. [DOI:10.1016/j.jff.2023.105671]

[63] Hu J, Tang J, Zhang X, Yang K, Zhong A, Yang Q, et al. Landscape in the gallbladder mycobiome and bacteriome of patients undergoing cholelithiasis with chronic cholecystitis. Front Microbiol. 2023; 14:1131694. [DOI:10.3389/fmicb.2023.1131694]

[64] Li W, Ren A, Qin Q, Zhao L, Peng Q, Ma R, et al. Causal associations between human gut microbiota and cholelithiasis: A mendelian randomization study. Front Cell Infect Microbiol. 2023; 13:1169119. [DOI:10.3389/fcimb.2023.1169119] [PMID]

[65] Yoshida S, Matsumoto H, Temmoku J, Shakespear N, Kiko Y, Kikuchi K, et al. Case report: Rapid development of amyloid A amyloidosis in temporal arteritis with SAA1. 3 allele; An unusual case of intestinal amyloidosis secondary to temporal arteritis. Front Immunol. 2023; 14:1144397. [DOI:10.3389/fimmu.2023.1144397]

[66] Kirkham JK, Estepp JH, Weiss MJ, Rashkin SR. Genetic variation and sickle cell disease severity: A systematic review and meta-analysis. JAMA Netw Open. 2023; 6(10):e2337484. [DOI:10.1001/jamanetworkopen.2023.37484] [PMID]

[67] Fu Q, Shen T, Yu Q, Jiang L, Yang R. Causal effect of gallstone disease on the risk of coronary heart disease or acute myocardial infarction: A Mendelian randomization study. Sci Rep. 2023; 13(1):18807. [DOI:10.1038/s41598-023-46117-9]

[68] Liu X, Qi X, Han R, Mao T, Tian Z. Gut microbiota causally affects cholelithiasis: A two-sample Mendelian randomization study. Front Cell Infect Microbiol. 2023; 13:1253447. [DOI:10.3389/fcimb.2023.1253447]

[69] Andrzejczak A, Karabon L. BTLA biology in cancer: From bench discoveries to clinical potentials. Biomark Res. 2024; 12(1):8. [DOI:10.1186/s40364-024-00556-2]

[70] Ke TM, Lophatananon A, Muir KR. An integrative pancreatic cancer risk prediction model in the UK biobank. Biomedicines. 2023; 11(12):3206. [DOI:10.3390/biomedicines11123206]

[71] Xue Y, Basturk O. Intraductal neoplasms of the pancreatobiliary tract: Navigating the alphabet. Histopathology. 2023; 83(4):499-508. [DOI:10.1111/his.15003]

[72] Mahmood F, Akingboye A, Malam Y, Thakkar M, Jambulingam P. Complicated acute cholecystitis: The role of C-reactive protein and neutrophil-lymphocyte ratio as predictive markers of severity. Cureus. 2021; 13(2):e13592. [DOI:10.7759/cureus.13592]

[73] Addissouky TA, Ali MM, Sayed IE, Wang Y. Emerging advanced approaches for diagnosis and inhibition of liver fibrogenesis. Egypt J Intern Med. 2024; 36(1):19. [DOI:10.1186/s43162-024-00283-y]

[74] Lee SJ, Kim HC, Kim SW, Won KY, Park SH, Jeong WK. Imaging and clinical findings of xanthogranulomatous inflammatory disease of various abdominal and pelvic organs: A pictorial essay. J Korean Soc Radiol. 2024; 85(1):109. [DOI:10.3348/jksr.2023.0026] [PMID]

[75] Arnott W, Hutchins J, Malhotra T, Ketheesan Y, Steinberg L, Carter L, et al. Xanthogranulomatous cholecystitis: Diagnostic complexity and review of the literature. J Surg Case Rep. 2023; 2023(6):rjad308. [DOI:10.1093/jscr/rjad308]

[76] Khafaji MA, Bagasi JT, Albahiti SK, Alsayegh LA, Alsayyad SA, Algarni SS, et al. Accuracy of ultrasound and computed tomography in diagnosing acute cholecystitis patients in a tertiary care center in Saudi Arabia. Cureus. 2023; 15(9):e44934. [DOI:10.7759/cureus.44934] [PMID]

[77] Arredondo Montero J, Pérez Riveros BP, Bueso Asfura OE, Rico Jiménez M, López-Andrés N, Martín-Calvo N. Leucine-rich alpha-2-glycoprotein as a non-invasive biomarker for pediatric acute appendicitis: A systematic review and meta-analysis. Eur J Pediatr. 2023; 182(7):3033-44. [DOI:10.1007/s00431-023-04978-2]

[78] Manudhane AP, Leupold MD, Shah HW, Shah R, Han SY, Lee PJ, et al. A review on endoscopic management of acute cholecystitis: endoscopic ultrasound-guided gallbladder drainage and endoscopic transpapillary gallbladder drainage. Medicina. 2024; 60(2):212. [DOI:10.3390/medicina60020212]

[79] Addissouky TA, Ali M, El Tantawy El Sayed I, Wang Y. Revolutionary Innovations in Diabetes Research: From Biomarkers to Genomic Medicine. Iran J Diabetes Obesity. 2023; 15(4):228-42. [DOI:10.18502/ijdo.v15i4.14556]

[80] Pourmadadi M, Holghoomi R, Shamsabadipour A, Malekibaladi R, Rahdar A, et al. Copper nanoparticles from chemical, physical, and green synthesis to medicinal application: A review. Plant Nano Biol. 2024; 8:100070. [DOI: 10.1016/j.plana.2024.100070]

[81] Addissouky TA, El Tantawy El Sayed I, Ali MMA, Wang Y, El Baz A, Elarabany N, et al. Shaping the future of cardiac wellness: exploring revolutionary approaches in disease management and prevention. J Clin Cardiol. 2024; 5(1):6-29. [DOI:10.33696/cardiology.5.048]

[82] Kumar A, Mohanty NR, Mohanty M, Dash S. Comparison of MRCP and ERCP in the evaluation of common bile duct and pancreatic duct pathologies. Front Med Technol. 2023; 5:946555. [DOI:10.3389/fmedt.2023.946555]

[83] Chen H, Wang J, Ji Q, Jiang Z. Sodium butyrate restricts neutrophils migration and NETs formation through reducing macrophage-derived CXCL16 in calculous cholecystitis. Heliyon. 2024; 10(3):e25189. [DOI:10.1016/j.heliyon.2024.e25189]

[84] Chacko AM, Hood ED, Zern BJ, Muzykantov VR. Targeted nanocarriers for imaging and therapy of vascular inflammation. Curr Opin Colloid Interface Sci. 2011; 16(3):215-27. [DOI:10.1016/j.cocis.2011.01.008] [PMID]

[85] Zan C, An J, Wu Z, Li S. Engineering molecular nanoprobes to target early atherosclerosis: Precise diagnostic tools and promising therapeutic carriers. Nanotheranostics. 2023; 7(3):327-44. [DOI:10.7150/ntno.82654] [PMID]

[86] Goyal AK, Ramchandani M, Basak T. Recent advancements, challenges, and future prospects in usage of nanoformulation as theranostics in inflammatory diseases. J Nanotheranostics. 2023; 4(1):106-26. [DOI:10.3390/jnt4010006]

[87] Liu Y, Deng S, Song Z, Zhang Q, Guo Y, Yu Y, et al. MLIF modulates microglia polarization in ischemic stroke by targeting eEF1A1. Front Pharmacol. 2021; 12:725268. [DOI:10.3389/fphar.2021.725268]

[88] Yan Q, Zhang S, Li S, Wang G, Zhang A, Jin T, et al. Cultivation and genomic characterization of the bile bacterial species from cholecystitis patients. Front Microbiol. 2021; 12:739621. [DOI:10.3389/fmicb.2021.739621] [PMID]

[89] Goyal PA, Bankar NJ, Mishra VH, Borkar SK, Makade JG. Revolutionizing medical microbiology: How molecular and genomic approaches are changing diagnostic techniques. Cureus. 2023; 15(10):e47106. [DOI:10.7759/cureus.47106] [PMID]

[90] Addissouky TA. Polyploidy-mediated resilience in hepatic aging: Molecular mechanisms and functional implication. Egypt Liver J. 2024; 14(1):1-14. [DOI:10.1186/s43066-024-00391-y]

[91] Addissouky TA, Khalil AA. Detecting lung cancer stages earlier by appropriate markers rather than biopsy and other techniques. Am J Clin Pathol. 2020; 154(Supplement_1):S146-7. [DOI:10.1093/ajcp/aqaa161.320]

[92] Yang XT, Wang J, Jiang YH, Zhang L, Du L, Li J, et al. Insight into the mechanism of gallstone disease by proteomic and metaproteomic characterization of human bile. Front Microbiol. 2023; 14:1276951. [DOI:10.3389/fmicb.2023.1276951]

[93] Wang L, Sun W, Chang Y, Yi Z. Differential proteomics analysis of bile between gangrenous cholecystitis and chronic cholecystitis. Med Hypotheses. 2018; 121:131-6. [DOI:10.1016/j.mehy.2018.07.004]

[94] Korbecki J, Bosiacki M, Chlubek D, Baranowska-Bosiacka I. Bioinformatic analysis of the CXCR2 ligands in cancer processes. Int J Mol Sci. 2023; 24(17):13287. [DOI:10.3390/ijms241713287] [PMID]

[95] Addissouky TA, El Agroudy AE, Khalil AA. Developing a novel non-invasive serum-based diagnostic test for early detection of colorectal cancer. Am J Clin Pathol. 2023; 160(Supplement_1):S17. [DOI:10.1093/ajcp/aqad150.037]

[96] Hall L, Halle-Smith J, Evans R, Toogood G, Wiggins T, Markar SR, et al. Ursodeoxycholic acid in the management of symptomatic gallstone disease: Systematic review and clinician survey. BJS Open. 2023; 7(2):zrac152. [DOI:10.1093/bjsopen/zrac152] [PMID]

[97] Guarino MP, Cong P, Cicala M, Alloni R, Carotti S, Behar J. Ursodeoxycholic acid improves muscle contractility and inflammation in symptomatic gallbladders with cholesterol gallstones. Gut. 2007; 56(6):815-20. [DOI:10.1136/gut.2006.109934] [PMID]

[98] Fickert P, Hirschfield GM, Denk G, Marschall HU, Altorjay I, Färkkilä M, et al. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. J Hepatol. 2017; 67(3):549-58. [DOI:10.1016/j.jhep.2017.05.009] [PMID]

[99] Lee YJ, Park YS, Park JH. Cholecystectomy is feasible in children with small-sized or large numbers of gallstones and in those with persistent symptoms despite medical treatment. Pediatr Gastroenterol Hepatol Nutr. 2020; 23(5):430-8. [DOI:10.5223/pghn.2020.23.5.430]

[100] Addissouky TA, El Tantawy El Sayed I, Ali MMA, Wang Y, El Baz A, Khalil AA, et al. Can vaccines stop cancer before it starts? assessing the promise of prophylactic immunization against high-risk preneoplastic lesions. J Cell Immunol. 2023; 5(4):126-7. [DOI:10.33696/immunology.5.178]

[101] Lone PA, Ahmed SW, Prasad V, Ahmed B. Role of turmeric in management of alveolar osteitis (dry socket): A randomised clinical study. J Oral Biol Craniofac Res. 2018; 8(1):44-7. [DOI:10.1016/j.jobcr.2017.08.005] [PMID]

[102] Dong ZY, Wang GL, Liu X, Liu J, Zhu DZ, Ling CQ. Treatment of cholecystitis with Chinese herbal medicines: A systematic review of the literature. World J Gastroenterol. 2012; 18(14):1689-94. [DOI:10.3748/wjg.v18.i14.1689] [PMID]

[103] Chawla A, Bosco JI, Lim TC, Srinivasan S, Teh HS, Shenoy JN. Imaging of acute cholecystitis and cholecystitis-associated complications in the emergency setting. Singapore Med J. 2015; 56(8):438-43. [DOI:10.11622/smedj.2015120] [PMID]

[104] Gupta P, Marodia Y, Bansal A, Kalra N, Kumar-M P, Sharma V, et al. Imaging-based algorithmic approach to gallbladder wall thickening. World J Gastroenterol. 2020; 26(40):6163-81. [DOI:10.3748/wjg.v26.i40.6163] [PMID]

[105] Brook OR, Kane RA, Tyagi G, Siewert B, Kruskal JB. Lessons learned from quality assurance: Errors in the diagnosis of acute cholecystitis on ultrasound and CT. Am J Roentgenol. 2011; 196(3):597-604. [DOI:10.2214/ajr.10.5170]

[106] Ahmed M, Nag HH, Meena P. Clinical approach to patients with thick wall gallbladder. Egypt J Radiol Nuclear Med. 2023; 54(1):184. [DOI:10.1186/s43055-023-01137-3]

[107] Zhang X, Yue P, Zhang J, Yang M, Chen J, Zhang B, et al. A novel machine learning model and a public online prediction platform for prediction of post-ERCP-cholecystitis (PEC). EClinicalMedicine. 2022; 48:101431. [DOI:10.1016/j.eclinm.2022.101431] [PMID]

[108] Wu B, Buddensick TJ, Ferdosi H, Narducci DM, Sautter A, Setiawan L, et al. Predicting gangrenous cholecystitis. HPB. 2014; 16(9):801-6. [DOI:10.1111/hpb.12226] [PMID]

[109] Fugazzola P, Cobianchi L, Di Martino M, Tomasoni M, Dal Mas F, Abu-Zidan FM, et al. Prediction of morbidity and mortality after early cholecystectomy for acute calculous cholecystitis: results of the S.P.Ri.M.A.C.C. study. World J Emerg Surg. 2023; 18(1):20. [DOI:10.1186/s13017-023-00488-6]

[110] Sachs GF, Ourshalimian S, Jensen AR, Kelley-Quon LI, Padilla BE, Shew SB, et al. Machine learning to predict pediatric choledocholithiasis: A western pediatric surgery research consortium retrospective study. Surgery. 2023; 174(4):934-9. [DOI:10.1016/j.surg.2023.07.008]

[111] Al-Abcha A, Radwan Y, Blais D, Mazzaferri Jr EL, Boudoulas KD, Essa EM, et al. Genotype-guided use of P2Y12 inhibitors: A review of current state of the art. Front Cardiovasc Med. 2022; 9:850028. [DOI:10.3389/fcvm.2022.850028]

[112] Wang SY, Yeh CN, Jan YY, Chen MF. Management of gallstones and acute cholecystitis in patients with liver cirrhosis: What should we consider when performing surgery? Gut Liver. 2021; 15(4):517-27. [DOI:10.5009/gnl20052] [PMID]

[113] Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, et al. Nutrigenetics and nutrigenomics: Viewpoints on the current status and applications in nutrition research and practice. J Nutrigenet Nutrigenomics. 2011; 4(2):69-89. [DOI:10.1159/000327772] [PMID]

[114] Addissouky TA. Liver stiffness as a dynamic predictor of decompensation and mortality in alcohol-related liver disease. Discov Med. 2024; 1(96). [DOI:10.1007/s44337-024-00083-x]

[115] Vimaleswaran KS. A nutrigenetics approach to study the impact of genetic and lifestyle factors on cardiometabolic traits in various ethnic groups: Findings from the GeNuIne Collaboration. Proc Nutr Soc. 2020; 79(2):194-204. [DOI:10.1017/S0029665119001186] [PMID]

[116] Lagoumintzis G, Patrinos GP. Triangulating nutrigenomics, metabolomics and microbiomics toward personalized nutrition and healthy living. Human Genomics. 2023; 17(1):109. [DOI:10.1186/s40246-023-00561-w]

[117] Weinsier RL, Ullmann DO. Gallstone formation and weight loss. Obes Res. 1993; 1(1):51-6. [DOI:10.1002/j.1550-8528.1993.tb00008.x] [PMID]

[118] Hernando-Redondo J, Toloba A, Benaiges D, Salas-Salvadó J, Martínez-González MA, Corella D, et al. Mid-and long-term changes in satiety-related hormones, lipid and glucose metabolism, and inflammation after a Mediterranean diet intervention with the goal of losing weight: A randomized, clinical trial. Front Nutr. 2022; 9:950900. [DOI:10.3389/fnut.2022.950900]

[119] Parra-Landazury NM, Cordova-Gallardo J, Méndez-Sánchez N. Obesity and gallstones. Visc Med. 2021; 37(5):394-402. [DOI:10.1159/000515545]

[120] Schirren J, Dietz W, Rothmund M. [Acute acalculous cholecystitis. A stress-induced complication (Germany)]. Chirurg. 1990; 61(5):382-6. [PMID]

[121] Addissouky TA, El Tantawy El Sayed I, Ali MMA, Alubiady MHS. Optical insights into fibrotic livers: Applications of near-infrared spectroscopy and machine learning. Arch Gastroenterol Res. 2024; 5(1):1-10. [DOI:10.33696/Gastroenterology.5.048]

[122] Addissouky TA, Ali MM, El Sayed IE, Wang Y, Khalil AA. Translational insights into molecular mechanisms of chemical hepatocarcinogenesis for improved human risk assessment. Adv Clin Toxicol. 2024; 9(1):294. [DOI:10.23880/act-16000294]

[123] Addissouky TA, Wang Y, El Tantawy El Sayed I, Majeed MA, Khalil AA. Emerging technologies and advanced biomarkers for enhanced toxicity prediction and safety pharmacology. Adv Clin Toxicol. 2024; 9(1):293.[DOI:10.23880/act-16000293]

[124] Addissouky TA, Wang Y, El Tantawy El Sayed I, Majeed MA, Khalil AA. Transforming toxicity assessment through microphysiology, bioprinting, and computational modeling. Adv Clin Toxicol. 2024; 9(1):295. [DOI:10.23880/act-16000295]

[125] Fu Y, Pang L, Dai W, Wu S, Kong J. Advances in the study of acute acalculous cholecystitis: A comprehensive review. Dig Dis. 2022; 40(4):468-78. [DOI:10.1159/000520025]

[126] Yoshida M, Takada T, Kawarada Y, Tanaka A, Nimura Y, Gomi H, et al. Antimicrobial therapy for acute cholecystitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg. 2007; 14(1):83-90. [DOI:10.1007/s00534-006-1160-y] [PMID]

[127] Suh SW, Choi YS, Choi SH, Do JH, Oh HC, Kim HJ, et al. Antibiotic selection based on microbiology and resistance profiles of bile from gallbladder of patients with acute cholecystitis. Sci Rep. 2021; 11(1):2969. [DOI:10.1038/s41598-021-82603-8] [PMID]

[128] Addissouky TA, El Sayed IE, Ali MM. Regenerating damaged joints: the promise of tissue engineering and nanomedicine in lupus arthritis. J Clin Orthop Trauma Care. 2024; 6(2):1-8. [DOI:10.31579/2694-0248/083]

[129] Addissouky TA. Translating molecular heterogeneity into precision medicine for advanced liver disease. Arch Gastroenterol Res. 2024: 5(1):47–58. [DOI: 10.33696/gastroenterology.5.054]

[130] Junaid M, Thirapanmethee K, Khuntayaporn P, Chomnawang MT. CRISPR-based gene editing in Acinetobacter baumannii to combat antimicrobial resistance. Pharmaceuticals. 2023; 16(7):920. [DOI:10.3390/ph16070920]

[131] Kharb S, Joshi A. Multi-omics and machine learning for the prevention and management of female reproductive health. Front Endocrinol. 2023; 14:1081667. [DOI:10.3389/fendo.2023.1081667]

[132] Babu M, Snyder M. Multi-omics profiling for health. Mol Cell Proteomics. 2023; 22(6):100561. [DOI:10.1016/j.mcpro.2023.100561] [PMID]

[133] Cianci P, Restini E. Management of cholelithiasis with choledocholithiasis: Endoscopic and surgical approaches. World J Gastroenterol. 2021; 27(28):4536-54. [DOI:10.3748/wjg.v27.i28.4536] [PMID]

[134] Jia Z, Peng J, Wan X, He P, Luo D. Endoscopic minimally invasive cholecystolithotomy in a patient with duplicate gallbladder: A case report. J Int Med Res. 2020; 48(4):300060519886973. [DOI:10.1177/0300060519886973] [PMID]

[135] Adir O, Poley M, Chen G, Froim S, Krinsky N, Shklover J, et al. Integrating artificial intelligence and nanotechnology for precision cancer medicine. Adv Mater. 2020; 32(13):e1901989. [DOI:10.1002/adma.201901989] [PMID]

[136] Das KP, J C. Nanoparticles and convergence of artificial intelligence for targeted drug delivery for cancer therapy: Current progress and challenges. Front Med Technol. 2023; 4:1067144. [DOI:10.3389/fmedt.2022.1067144] [PMID]

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