

# COVID-19 Associated Pancreatitis: A Review of 66 Cases

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## Research article

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## Abstract

**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown itself with different clinical manifestations. Besides respiratory distress, cough, and fever, which were the most common symptoms, pancreatitis has been reported as a rare presentation of this disease, but the knowledge on this association and its pathogenesis is sparse.

**Methods:** Four databases, including Pub Med, Scopus, Web of Science, and Google Scholar, were searched for the association of pancreatitis and SARS-CoV-2 infection, and 29 relevant articles were extracted and reviewed.

**Results:** We reviewed 29 studies provided 66 cases developed acute pancreatitis while they were infected with SARS-CoV-2. The mean age of patients was  $49.94 \pm 16.96$ . The female to male ratio was 1.06 (33 to 31). In 44% of cases, acute pancreatitis developed as the primary presentation of Coronavirus Disease 2019 (COVID-19) and 9% of reported cases, expired.

**Conclusions:** During this pandemic, SARS-CoV-2 should be considered in the differential diagnosis of the patients presenting with acute pancreatitis. Although pancreatitis will respond to standard care, these patients need isolation and observation for later development of respiratory symptoms.

## Background

Coronavirus disease 2019 (COVID-19) emerged in Wuhan city in December 2019, and rapidly involved almost all countries and territories in the world (1, 2). The most common manifestations of this disease include fever, cough, dyspnea, sore throat, headache, and myalgia (3). Although it mainly involves the respiratory system, many studies have reported various extrapulmonary manifestations such as acute cardiac injury, heart failure, cardiac arrhythmia, acute ischemic stroke, cerebral venous thrombosis, encephalitis, and gastrointestinal symptoms (4-8). Digestive manifestations such as anorexia, nausea, vomiting, abdominal pain, diarrhea can range from mild to severe in their presentation. There are reports of more severe complications which may need urgent interventions including bowel ischemia and hepatic necrosis (9, 10). Acute pancreatitis is a relatively rare presentation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (6). Pancreatitis has been reported with several different types of viruses through diverse mechanisms (11). It seems that the coronavirus can also affect the pancreas and cause pancreatic injury (12). The mechanism of pancreatitis in the course of COVID-19 is not entirely known.(13)

In recent months, publications have reported acute pancreatitis as a COVID-19 manifestation. This study gives a detailed review of relevant articles and summarizes their findings to clarify acute pancreatitis features induced by COVID-19.

## Methods

This literature review was performed through a comprehensive search in three databases, including Pub Med, Scopus, and Web of Science. English articles about the association of SARS-CoV-2 and pancreatitis, published before 30<sup>th</sup> of October 2020, were included in this review. We also searched Google Scholar or the grey literature and examined the first 100 results. The search strategy employed for each database is shown in Table 1.

All of the citations were imported to Endnote X9 software (Clarivate Analytics, USA), and all duplicates were excluded. Then we carried out the first screening, and irrelevant articles were excluded according to their titles and abstracts. In the next step, full-text screening was performed to detect the eligible studies. Finally, an Excel (Microsoft, Redmond, WA, USA) spreadsheet was used to extract the key findings of the studies. All steps were done by two authors separately. In case of disagreements, a third person was consulted.

## Results

We identified 73, 117, 51, 17 records in Pub Med, Scopus, Web of Science, and Google Scholar, respectively. After removing duplicates and screening, we found 29 publications (Figure 1), including 27 case reports and 2 cohort studies. Taken together, 66 patients with COVID-19 associated pancreatitis were reported. Table 2 represents the key characteristics of the cases. In terms of geographical location, nine studies (33.3 %) were from Asia, eight studies (29.6%) were from Europe, seven studies (25.9%) were from North America, two studies (7.4%) were from South America, and one study (3.7%) was from Africa. In total, the female to male ratio was 1.06 (33 to 31); gender was not mentioned in two cases (14, 15). The mean age of patients (n=66) was  $49.94 \pm 16.96$ . Reviewed records indicated that in 44% of patients, acute pancreatitis presented as the initial manifestation of COVID-19. No significant past medical or surgical history was reported for 35% of cases. Among underlying disease reported in 65% of patients, hypertension was the most common. In a cohort study conducted by Inamdar et al., thirty-two COVID-19 positive patients with pancreatitis were reported. Idiopathic pancreatitis accounts for the majority of these cases. Gallstone, alcohol, and drugs were responsible for 16%, 6%, and 3% of pancreatitis in these patients, respectively (16). The mortality rate was 9% among all patients reported in the studies.

## Discussion

### Pathogenicity:

Studies have suggested a causal relationship between SARS-CoV-2 infection and acute pancreatitis (17, 18). Pancreatic injury may emerge directly due to viral replications, or it may be due to inflammatory processes and immune dysregulation caused by COVID-19 (12, 17-20).

As mentioned earlier, SARS-CoV-2 pathogenicity for acute pancreatitis is not clear yet (13). Investigations have reported several mechanisms that explain pancreatic involvement during this disease. One of these mechanisms is based on Angiotensin-converting enzyme 2 (ACE2) receptor expression on the

pancreatic cells (21). The pathogenicity of SARS-CoV-2 is through binding to the ACE2 receptor on alveolar cells in the lung (22). ACE2 receptor is also present on other organs such as the pancreas (23). According to this fact, the pancreatic tropism of the COVID-19 virus could be justified.

#### **Timing of pancreatitis presentation:**

The onset of pancreatitis presentations varied among studied cases. In some cases, acute pancreatitis was presented as the initial manifestation of COVID-19. In other ones, pancreatic injury developed from days to weeks after the emergence of respiratory symptoms. Evidently, the time of emerging pancreatitis presentations has not the same pattern in different patients.

#### **Diagnosis:**

COVID-19 can involve the gastrointestinal tract and may lead to pancreatic enzyme elevation (11, 24). Although pancreatic enzyme elevation is one of the diagnostic criteria for acute pancreatitis, rising pancreatic enzymes is possible in infected patients in the absence of any pancreatitis presentations (25, 26). Therefore, in addition to the enzyme elevation, at least one of the following criteria should be considered in the diagnosis of acute pancreatitis in patients with COVID-19: characteristic acute pain in epigastric or right upper quadrant and abdominal imaging in favor of acute pancreatitis (26).

In the reviewed studies, pancreatic enzyme levels were detected from normal (27) to above 20 to 30 times more than the normal range (19, 28). In addition to that, the C-Reactive Protein (CRP) level also was up to 20-times elevated (17). The most common pancreatitis presentation was sudden onset epigastric pain, which was reported mild to severe in different individuals. Other manifestations such as anorexia, nausea, vomiting, diarrhea, fever varied among patients. In one study, no abdominal symptoms were reported, and investigations to confirm acute Pancreatitis were done just due to persistent fever (14).

Acute pancreatitis was confirmed through abdominal imaging, especially Computed Tomography (CT) scans in the majority of the studies. The most common imaging findings in publications were peripancreatic fat stranding and fluid collection. Necrotizing pancreatitis, pancreatic fluid collection, and pancreatic pseudocyst were also reported (29-32). Although it is not a common procedure, in one study pseudocyst sample was tested positive for SARS-CoV-2 (33). Ultrasonography was also a standard modality to exclude cholelithiasis as a common reason for pancreatitis.

#### **Treatment and outcomes:**

After confirming the diagnosis of the COVID-19, nearly all cases of COVID-19 associated pancreatitis were treated by two main strategies: (1) Treatment of COVID-19, which is supportive care in most cases or can include antiviral and anti-inflammatory drugs based on patients' conditions and each country guideline. (2) Treating pancreatitis as routine (fluid resuscitation, analgesics, and antibiotics if indicated). Considering these treatments, the symptoms of most of the cases were resolved.

## **Limitations**

Although we reviewed databases thoroughly, the infancy of the publications could impact our study.

## **Conclusion**

Based on this review, we strongly recommend that during this pandemic, it should be borne in mind that every patient with pancreatitis presentations can be a possible case of COVID-19. Although pancreatitis will respond to standard care, these patients need isolation and observation for later development of respiratory symptoms.

## **Abbreviations**

COVID-19: Coronavirus Disease 2019, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, US: Ultrasonography, CT scan: Computed Tomography scan, ACE2: Angiotensin-converting enzyme 2

## **Declarations**

#### **Ethics approval and consent to participate**

Not applicable

#### **Consent for publication**

Not applicable

#### **Availability of data and materials**

Not applicable

#### **Competing interests**

The authors declare that they have no competing interests.

#### **Funding**

Not applicable

### Authors' contribution

ZR: study design, data collection, manuscript preparation. AA: data collection, analysis, manuscript preparation. AF: Data collection, manuscript preparation, KBL: conceptualized the study, manuscript preparation. All authors read and approved the final manuscript.

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## Tables

Table 1. Search strategies

Database	Search strategy
Pub med	((coronavirus[MeSH Terms] or coronavirus[Title/Abstract] OR COVID-19*[Title/Abstract] OR SARS-Cov-2*[Title/Abstract] OR 2019-nCoV*[Title/Abstract] OR 2019 novel coronavirus[Title/Abstract] OR coronavirus disease*[Title/Abstract])) AND (pancreatitis[Title/Abstract] OR pancreatitis[MeSH Terms] OR "acute pancreatitis"[Title/Abstract] )
Scopus	(INDEXTERMS ("coronavirus") OR TITLE-ABS-KEY ("coronavirus" or "COVID-19*" OR "SARS-Cov-2*" OR "2019-nCoV*" or "2019 novel coronavirus*" or "coronavirus disease*")) AND (INDEXTERMS("pancreatitis") OR TITLE-ABS-KEY ("pancreatitis" OR "acute pancreatitis"))
Web of science	(TS= ("coronavirus" or "COVID-19*" OR "SARS-Cov-2*" OR "2019-nCoV*" or "2019 novel coronavirus" or "coronavirus disease*")) AND (TS= ("pancreatitis" OR "acute pancreatitis"))

Table 2. Key findings of the studies

Table 2. Key findings of the studies	Type of study	Age and sex	Past medical and surgical history	Pancreatitis presentations (CC, P/E)	Enzyme elevation	CRP elevation	Abdominal imaging	The onset of pancreatitis symptoms
Author(s)								
Alloway et al. (32)	Case Report	7-year-old girl	-	Abdominal pain, anorexia, and then two weeks later, abdominal pain, fever, non-bloody, non-bilious vomiting, left lower quadrant, and epigastric pain.  Distension, tenderness to palpation in the left upper and left lower quadrant, and epigastric region, fullness noted in the left upper quadrant	+	N	Abdominal Ultrasound (US) and Computed Tomography (CT) scan were suggestive of necrotizing Pancreatitis	Presented as Pancreatitis
Aloysius et al. (34)	Case report	36-year-old woman	Chronic anxiety, obesity	Nausea, vomiting, diarrhea,  severe stabbing epigastric pain radiating to back, severe epigastric tenderness	+	+	CT scan: unremarkable pancreas	Six days after respiratory symptoms
Alves et al. (35)	Case report	56-year old woman	HTN, minimal alcohol consumption	Epigastric pain on admission but no relevant abdominal symptoms during hospitalization	+	N	Chest CT: tail parenchymal enlargement and surrounding retroperitoneal fat stranding of the pancreas.  MRCP: acute Pancreatitis, diffusely enlarged pancreas  The endoscopic US showed no microlithiasis.	Amylase and lipase elevated during hospitalization. The timing was not mentioned
Bokhari and Mahmood. (29)	Case report	32-year-old man	-	Severe mid epigastric pain radiating to back, intermittent fever, chills, non-biliary vomiting	+	+	US: unremarkable  CT scan: a bulky and  swollen pancreas with significant peripancreatic inflammatory changes and fluid collection along the gastrosplenic ligament.	Fourteen days after respiratory symptoms

Table 2. Key findings of the studies	Type of study	Age and sex	Past medical and surgical history	Pancreatitis presentations (CC, P/E)	Enzyme elevation	CRP elevation	Abdominal imaging	The onset of pancreatitis symptoms
Author(s)								
Brikman et al. (36)	Case report	61-year-old man		Sudden diffuse abdominal pain with anorexia. No fever, no vomiting, or diarrhea.  the abdomen was soft, with mild diffuse tenderness	+	N	CT scan: focal parenchymal enhancement of the pancreas head with inflammatory changes in peripancreatic fat suggestive of acute Pancreatitis.	14 <sup>th</sup> day of admission  19 days after developing a fever, dyspnea, and cough
Charra et al. <sup>(14)</sup>	Case report	67-year-old (gender was not mentioned)	Cholecystectomy, DM type 2, obesity	Without any abdominal symptoms on admission (the patient intubated on the 5th day of admission); investigations were due to persistent fever	+	+	CT scan: stage C pancreatitis according to the Balthazar classification  US: unremarkable	13 <sup>th</sup> day of admission (persistent fever)
Cheung et al. (37)	Case report	38-year-old man	-	Fever, severe epigastric pain, nausea, and vomiting. One week after discharge, the patient returned to the ED complaining of recurrent sharp epigastric pain with radiation to the back, nausea and vomiting. On the second time, a physical examination revealed moderate tenderness to light palpation in the epigastric region	+	N	US: unremarkable  CT scan: acute Pancreatitis  MRCP and MRI of the abdomen showed evidence of acute Pancreatitis and normal gallbladder.	One week after a positive test for COVID-19 (symptoms were not mentioned), gastrointestinal symptoms started.

Table 2. Key findings of the studies	Type of study	Age and sex	Past medical and surgical history	Pancreatitis presentations (CC, P/E)	Enzyme elevation	CRP elevation	Abdominal imaging	The onset of pancreatitis symptoms
Author(s)								
Dietrich et al. (38)	Case report	72-year-old man	HTN, Overweight BMI 29.4 kg/m2	Nausea and mild abdominal pain.  The abdomen was bloated and tender, with diffuse pain	+	+	US: cholecystolithiasis, but  no signs of obstructive cholestasis. The pancreas was barely visible, but the parenchyma seemed to be inhomogeneous.  Endo US showed inhomogeneous pancreatic tissue without any  focal mass. A lean bile duct with no signs of an intraluminal stone or papilla passage of a stone was seen.  Abdominal CT was normal.	Presented as Pancreatitis
Fernandes et al.(30)	Case report	36-year-old woman	-	Intense upper abdominal pain, tachycardia	+	N	CT scan: signs of acute interstitial edematous Pancreatitis with an acute peripancreatic fluid collection.  US: unremarkable	Two days after onset of fever, cough, and dyspnea
Hadi et al.(17)	Case report	47-year-old woman		Fever, headache, and neck pain for one week and anorexia, sore throat, and dyspnea for a couple of days (does not have a specific abdominal pain)	+	+	US: acute Pancreatitis  with a diffusely voluminous pancreas without focal lesions or gallstones	In the course of admission

Table 2. Key findings of the studies	Type of study	Age and sex	Past medical and surgical history	Pancreatitis presentations (CC, P/E)	Enzyme elevation	CRP elevation	Abdominal imaging	The onset of pancreatitis symptoms
Author(s)								
Hadi et al. <sup>(17)</sup>	Case report	68-year-old woman	HTN, hypothyroidism, osteoporosis	Epigastric pain, fever, vomiting, diarrhea, fatigue, polydipsia abdominal pain and slight abdominal distension  physical examination showed direct epigastric and periumbilical tenderness	+	+	-	6 <sup>th</sup> day of admission
Inamdar et al. <sup>(16)</sup>	retrospective observational cohort study	18 women 14 men  Mean age :53.44 ± 16.60	Ten had DM. Fifteen had HTN.  Two had congestive heart failure.	All of the patients met all three of the following criteria: 1) lipase greater than three times the upper limit of normal, 2) cross-sectional imaging (CT or MRI) indicative of Pancreatitis, and 3) characteristic upper abdominal pain at admission	N	N	-	-
Karimzadeh et al. <sup>(39)</sup>	Case report	65-year-old woman	Asthma, HTN	Upper abdominal pain, constant nausea, chills, and myalgia for five days. the dry mucous membrane, pallor, and mild tenderness on the right upper quadrant of the abdomen	+	N	CT scan: unremarkable	Two days after chills and myalgia
Katarina et al. <sup>(40)</sup>	Case report	49-year-old woman	-	Severe epigastric pain radiating to back, nausea and one episode of vomiting containing food particles, epigastric tenderness	+	+	CT scan: edematous pancreas with diffuse enlargement and ill-defined border  US: unremarkable	2 <sup>nd</sup> day of Admission (5 days after respiratory symptoms)

Table 2. Key findings of the studies	Type of study	Age and sex	Past medical and surgical history	Pancreatitis presentations (CC, P/E)	Enzyme elevation	CRP elevation	Abdominal imaging	The onset of pancreatitis symptoms
Author(s)								
Kumaran et al. (31)	Case report	67-year-old woman	Small bowel resection and anastomosis due to superior mesenteric artery stenosis, HTN	Epigastric pain, diarrhea, and vomiting	+	+	CT scan: extensive peripancreatic fluid collection  CT angiogram: interval progression of previously seen peripancreatic inflammatory changes and non-enhancement of most of the head and proximal body (necrotizing Pancreatitis  US: unremarkable	One day before admission
Kurihara et al. (15)	Case report	55-year-old patient		Abnormalities of pancreatic enzymes were found in a routine blood test. Due to intubation, the patient was not able to express symptoms associated with Pancreatitis	+	+	US: unremarkable  CT scan: suggestive of acute Pancreatitis.	14 days after onset of symptoms (fever, cough)  6 <sup>th</sup> day of admission
Lakshmanan et al. (41)	Case report	68-year-old man	DM, HTN, chronic kidney disease stage IV	Persistent nausea, vomiting, and anorexia, but no abdominal pain	+	N	CT scan: peripancreatic fat stranding, especially around the tail, with mild duodenal wall thickening and adjacent fat stranding	Few days after admission
Mazrouei et al. (42)	Case report	24-year-old man	-	Non-radiating sharp, epigastric pain for the last two days. Nausea and vomiting,  soft abdomen with epigastric discomfort on palpation	+	N	CT scan: mild edema of the distal pancreas with a non-encapsulated peripancreatic low-density fluid around pancreatic tail extending to the splenorenal recess.	Two days before admission
Meireles et al. (11)	Case report	36-year-old woman	post-HELLP syndrome chronic kidney disease stage V, arterial HTN	Nausea, vomiting, and a belt-like epigastric pain without other specific findings	+	+	CT angiogram: no ischemic changes.  US: unremarkable	11 day after dry cough, breathlessness, and fever  (on the 7 <sup>th</sup> day of admission)
Meyers et al. (28)	Letters to the Editor	67-year-old Man	HTN, cholecystectomy, alcohol consumption	Sudden onset epigastric abdominal discomfort, tachycardia, fever, and  epigastric tenderness	+	-	CT scan: interstitial edematous Pancreatitis with moderate peripancreatic stranding and edema	Three days before developing fever and dyspnea

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Author(s)								
Miao et al. <sup>(43)</sup>	Letters to the Editor	26-year-old woman	-	Severe vomiting, epigastric pain, and fever	+	+	CT scan: enlarged pancreas gland without any structural abnormality. Gastrointestinal endoscopy revealed unspecific pan gastritis.	At least 7 days before confirming COVID-19
Patnaik et al. <sup>(19)</sup>	Case report	29-year-old man	-	Acute diffused abdominal pain radiating to the back and progressively worsened, low-grade fever, tachypnea, abdominal tenderness, which was maximal in the umbilical region.	+	+	US: bulky pancreas with irregular edematous margins, some peripancreatic fluid.  CT scan confirmed these findings.	Two days after developing dyspnea
Purayil et al. <sup>(44)</sup>	Case report	58-year-old man	-	Fever and vomiting for three days, epigastric pain, mild epigastric tenderness	+	+	US: unremarkable	-
Rabice et al. <sup>(45)</sup>	Case report	36-year-old pregnant woman	Asthma, cholecystectomy DM type 1, maternal obesity, pre-eclampsia in previous pregnancies,	Fever, nausea, vomiting, , epigastric pain and epigastric tenderness	+	N	US: unremarkable	Six days after respiratory symptoms
Schepis et al. <sup>(33)</sup>	Case report	67-years-old woman	recent hospitalization for interstitial edematous acute Pancreatitis of unknown origin.	Upper quadrant abdominal pain, fever, and vomiting. Abdominal distention, slight tenderness, and pain in epigastric and mesogastric regions. The pancreatic pseudocyst sample resulted positive for all three target genes of SARS-CoV2 researched	+	-	CT scan: the presence of a large pancreatic pseudocyst  (16 cm _ 8 cm x 12 cm) causing a partial stomach outlet obstruction.	Presented as Pancreatitis
Shinohara et al. <sup>(46)</sup>	Letters to the Editor	58-year-old man	HTN	Recurrent fever, intermittent abdominal pain	+	+	CT scan: enlargement of the pancreas with peripancreatic fat.	22 <sup>nd</sup> day after hospitalization

Table 2. Key findings of the studies	Type of study	Age and sex	Past medical and surgical history	Pancreatitis presentations (CC, P/E)	Enzyme elevation	CRP elevation	Abdominal imaging	The onset of pancreatitis symptoms
Author(s)								
Stevens et al. (47)	Case report	10-year-old girl	Asthma, obesity	Diffuse abdominal pain radiating to back and right lower quadrant pain fever, non-bloody, non-bilious vomiting, watery diarrhea, and anorexia	+	+	CT scan: inflammatory change within the peripancreatic fat; pancreas appeared prominent	Five days before admission
Szatmary et al. (48)	Retrospective cohort	Five men mean age:42	One of the patients had asthma	All patients had typical pain for Pancreatitis	+	N	CECT in all patients showed transient moderate to severe hepatic steatosis and mild pancreatic edema  US: unremarkable	On admission
Wang, K et al. (27)	Case report	42-year-old man	-	Nausea, persistent upper abdominal pain with radiation to the back	+	+	CT scan: enlargement of the pancreas and peripancreatic fluid accumulation, without biliary dilatation or microlithiasis.	Four days before chest discomfort and shortness of breath.
Wang, K et al. (27)	Case report	35-year-old man	-	Upper abdominal pain with radiation to the back, nausea, and vomiting	+	+	CT scan: showed pancreatic swelling, peripancreatic fluid accumulation, and prerenal fascial thickening	Five days before confirming COVID-19.
Zhao et al. (49)	Case report	62-year-old woman	HTN, DM type 1 Overweight BMI: 26.67 kg/m <sup>2</sup>	Abdominal distension and epigastric pain after breakfast  Mild abdominal tenderness without rebound tenderness	+	N	CT scan: exudative changes in pancreatic uncinata process and infiltration along the perivascular.	15 days after fever, cough, and fatigue  14 <sup>th</sup> day of admission

N: not mentioned, US: Ultrasonography, CT: Computed Tomography

## Figures

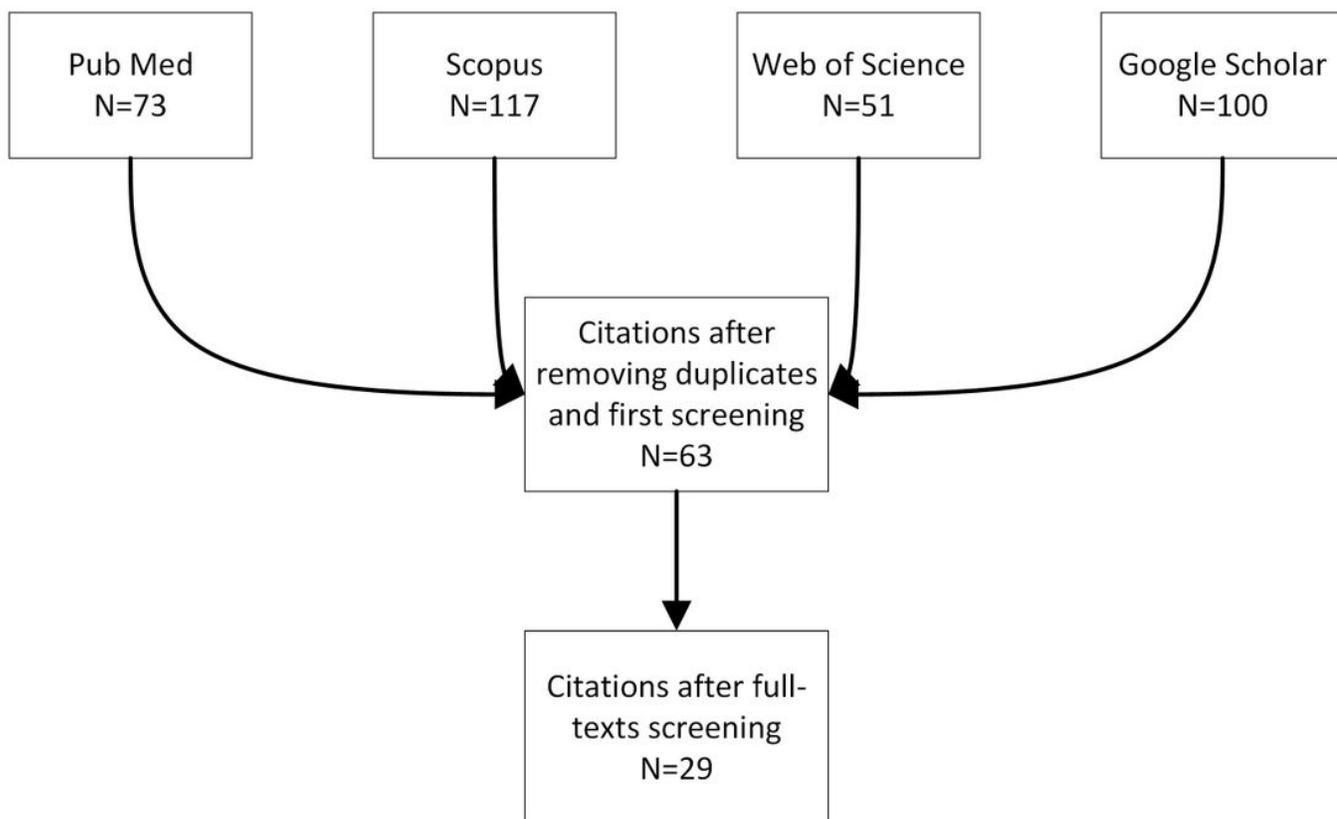


Figure 1

Review flow-diagram

## Supplementary Files

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- [PRISMA2009checklist.doc](#)