

# World Journal of *Gastrointestinal Oncology*

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2016-2019

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*WJGO* covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Pancreatic injury in patients with septic shock: A literature review

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### Abstract

Sepsis and septic shock are life threatening condition associated with high mortality rate in critically-ill patients. This high mortality is mainly related to the inadequacy between oxygen delivery and cellular demand leading to the onset of multiorgan dysfunction. Whether this multiorgan failure affect the pancreas is not fully investigated. In fact, pancreatic injury may occur because of ischemia, overwhelming inflammatory response, oxidative stress, cellular apoptosis and/or metabolic derangement. Increased serum amylase and/or lipase levels are common in patients with septic shock. However, imaging test rarely reveal significant pancreatic damage. Whether pancreatic dysfunction does affect the prognosis of patients with septic shock or not is still a matter of debate. In fact, only few studies with limited sample size assessed the clinical relevance of the pancreatic injury in this group of patients. In this review, we aimed to describe the epidemiology and the physiopathology of pancreatic injury in septic shock patients, to clarify whether it requires specific management and to assess its prognostic value. Our main finding is that pancreatic injury does not significantly affect the outcome in septic shock patients. Hence, increased serum pancreatic enzymes without clinical features of acute pancreatitis do not require further imaging investigations and specific therapeutic intervention.

**Key words:** Septic shock; Pancreas; Lipase; Amylase; Prognosis

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**Core tip:** Pancreatic injury is common in septic shock patients. Tissue hypoperfusion is the main leading cause of pancreatic insult. Other factors such as oxidative stress



and cellular apoptosis have been reported to enhance the pancreatic damage. The clinical relevance of increased level of pancreatic enzymes is not well established. In fact, hyperamylasemia and/or hyperlipasemia are not associated with higher mortality. Moreover, most of the imaging investigations do not show significant morphological changes of the pancreas. Hence, disturbed serum pancreatic enzymes without clinical evidence of acute pancreatitis should not trigger any specific therapy.

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## INTRODUCTION

Severe sepsis and septic shock are common life-threatening conditions in critically-ill patients<sup>[1-3]</sup>. Despite recent therapeutic advances and the establishment of internationally accepted guidelines regarding the management of patients suffering from septic shock, the overall mortality in these patients ranges from 30% to 60%<sup>[2,4,5]</sup>. This high mortality is usually associated with the onset of multiple organ dysfunction. In fact, a few studies have reported that the worsening of organ function as well as the increase in the number of the failing organs is significantly associated with poor outcome in both adult and pediatric patients<sup>[6,7]</sup>. Accordingly, it has been reported that the onset of acute kidney injury is associated with a significant rise in the intensive care unit (ICU) mortality up to 50%-70% and that the highest mortality has been in patients with a high score on the severity of illness scale and/or in those who require renal replacement therapy<sup>[2,8-10]</sup>. Similarly, hypoxic liver injury in patients with septic shock has been reported to be associated with a mortality as high as 50%<sup>[11,12]</sup>. Experimental and clinical studies also suggest that gut ischemia is one of the hallmarks of septic shock<sup>[13-15]</sup>. However, whether pancreatic exocrine function is also impaired in septic shock patients has not been fully investigated. Moreover, there is still debate regarding the optimum modality for management of pancreatic insult as well as its prognostic value.

The aim of this review is to describe the epidemiology and the physiopathology of pancreatic injury in septic shock patients, to clarify whether it requires specific management and to assess its prognostic value.

## RESEARCH

A systematic literature search was conducted through Pubmed by using the following Medical Subheadings terms: Septic shock, sepsis, lipase, amylases and acute pancreatitis. Different Boolean operator combinations

(AND/OR) were attempted. Overall, 97 articles were selected for this review. We didn't proceed to any language restriction and only the studies published between 1996 and 2016 were considered.

## EPIDEMIOLOGY OF PANCREATIC INJURY IN SEPTIC SHOCK

The incidence of pancreatic injury in critically-ill patients is extremely variable according to the used definition. High levels of amylase levels have been reported in 32% to 79% of patients admitted in medical or surgical ICUs<sup>[16-19]</sup>. However, most of these studies have concluded that this elevation is not always due to pancreatic insults<sup>[16,18]</sup>. In fact, the proportion of non-pancreatic isoamylase in patients with hyperamylasemia has been reported to range from 30% to 74% of the total serum amylase<sup>[16,18]</sup>. Hence, other markers have been used to assess the exocrine pancreatic dysfunction in critically-ill patients. Lipase is one such marker which is more specific for the diagnosis of pancreatitis<sup>[20]</sup>. Similar to hyperamylasemia, increased lipase serum level is also common in critically-ill patients. In fact, Manjuck *et al.*<sup>[21]</sup> reported that hyperlipasemia is found in 40% of the patients requiring ICU admission. Similarly, Denz *et al.*<sup>[19]</sup> reported increased serum lipase levels in 57% of critically-ill patients. Recent guidelines have highlighted that the rise of one or both of these two enzymes should be higher than three times the upper limit of normal range to be considered as a useful criterion for acute pancreatitis<sup>[22]</sup>. However, only a limited number of patients admitted to the ICU with a diagnosis other than pancreatitis fulfill this definition<sup>[23]</sup> and/or have significant morphological changes in pancreatic anatomy on imaging tests<sup>[19,21]</sup>. Only a few studies have focused on the exocrine pancreatic dysfunction in the subgroup of critically-ill patients with septic shock<sup>[23-25]</sup>. Hence, epidemiological data regarding the pancreatic function impairment in this group of patient is lacking.

## PHYSIOPATHOLOGY OF PANCREATIC INJURY IN SEPTIC SHOCK

The pathophysiology of pancreatic injury in septic shock patients is not fully understood. The most commonly accepted hypothesis is pancreatic ischemia<sup>[26,27]</sup>. However, few experimental and human studies have suggested that other mechanisms might also be involved such as cell apoptosis<sup>[28,29]</sup>, increased release of nitric oxide by the endothelial cells<sup>[30]</sup>, platelets activation<sup>[31]</sup>, ischemia - reperfusion phenomenon<sup>[32]</sup>, elevated triglyceride levels and the development of biliary sludge<sup>[33]</sup>.

### Pancreatic ischemia

Severe hypotension and tissue hypoperfusion are the main hallmarks of septic shock<sup>[34,35]</sup>. Experimental studies have shown that gut perfusion is severely impaired in the early stages of septic shock<sup>[14,36]</sup>. In a porcine model of septic shock caused by fecal peritonitis, Ijungdahl *et al.*<sup>[14]</sup>

have reported that the oxygen consumption of the gut, including that of pancreas, is markedly increased in this condition. This is accompanied by a significant decrease in the gut intramucosal pH which occurs even before the lactate rises in the arterial blood. The pancreas is particularly sensitive to hypotension. In fact, a temporary ischemia for 40 min has been shown to be sufficient to cause significant pancreatic injury on histological examination, presenting mainly as peripheral necrosis of the lobules<sup>[37]</sup>. Several studies have suggested that the impairment of pancreatic perfusion is more pronounced in septic shock. In fact, in an experimental animal model study, Raper *et al.*<sup>[26]</sup> reported that the cardiac output is increased during the hyper dynamic phase of septic shock. Concomitantly, the systemic blood flow is increased in the gallbladder and the colon whereas it is markedly decreased in the pancreas. This demonstrates that the oxygen delivery to the pancreatic cells is significantly decreased despite the considerable increase of their oxygen requirement<sup>[26]</sup>.

Beside these macro-circulatory abnormalities, pancreatic injury related to septic shock can also be explained by micro-circulatory and cellular dysfunctions<sup>[38]</sup>. In fact, severe sepsis and septic shock are commonly associated with coagulation abnormalities, usually manifested as disseminated intravascular coagulation<sup>[39,40]</sup>. Several forensic studies have reported ischemic and necrotic changes in various organs. These include occlusion and fibrin deposition in small and mid-size vessels, observed in patients who die from septic shock<sup>[41]</sup>. These abnormalities are triggered mainly by an overwhelming inflammatory reaction which is orchestrated by the immune host defense in response to the endotoxin aggression<sup>[34,39]</sup>. The expression of the tissue factor by the mononuclear, polymorphonuclear and endothelial cells activates the coagulation cascade<sup>[42,43]</sup>. Activation of platelets, down-regulation of anticoagulant pathways and reduced fibrin removal due to inhibition of fibrinolysis enhances microvascular thrombosis<sup>[39]</sup>. Experimental studies have shown that the pancreatic microcirculation is deeply disturbed in septic shock. In fact, in a model of fecal peritonitis, Hildebrand *et al.*<sup>[27]</sup> reported that the microcirculatory flow is reduced by 50% in various splanchnic organs within 240 min. The flow normalizes after fluid resuscitation in all the organs, except in the pancreas.

Although the most widely accepted hypothesis used to explain pancreatic dysfunction in patients with septic shock is pancreatic ischemia, significant pancreatic injury has also been reported in normotensive sepsis model. This suggests that other mechanisms may also be responsible for causing pancreatic ischemia<sup>[44]</sup>.

### Cellular apoptosis

Delayed and inappropriate management of septic shock is associated with a worse outcome due to multiple organ dysfunction syndrome (MODS)<sup>[45-48]</sup>. The main cause of MODS in this condition is the uncontrolled inflammatory storm caused by overwhelming host

immune response<sup>[49]</sup>. Beside the deleterious effect of this reaction on the macrocirculation and microcirculation, as described above, the pro-inflammatory cytokines—mainly interleukine (IL)-1 $\beta$ , IL-6 and tumor necrosis factor (TNF)- $\alpha$  - also activate the NF- $\kappa$ B pathway. This causes cellular self-destruction and apoptosis<sup>[50]</sup>. This has been demonstrated in the hepatocytes and the immune cells with severe Gram-negative bacterial infection<sup>[50,51]</sup>. Experimental studies have shown that the exposure of pancreatic cells to lipopolysaccharide is associated with apoptosis and increased release of TNF- $\alpha$ , IL-1 $\beta$  and IL-8. Damage to the Acinar cells consists of nuclear fragmentation, abnormal cytoplasmic vacuoles and cellular swelling<sup>[28,29,52,53]</sup>. Unlike these experimental studies, there is no evidence to suggest that apoptosis is a major cause of exocrine pancreatic dysfunction in patients suffering from septic shock. In fact, histological studies performed in patients who died from septic shock and multiorgan failure have shown that the apoptosis of acinar cells is seen only in a scattered manner<sup>[54]</sup>.

### Other mechanisms

Other hypothesis that may explain pancreatic injury in patients suffering from septic shock.

**The oxidative stress:** Oxidative stress has been demonstrated in patients suffering from septic shock patients<sup>[55]</sup>. The main causes of mitochondrial dysfunction and increased release of reactive oxygen species are ischemia/reperfusion phenomenon and inflammation<sup>[55,56]</sup>. Other factors, such as the activation of the phagocytic cells and the production of nitric oxide by the endothelial cells, have been shown to aggravate the oxidative stress<sup>[57]</sup>. The cellular damage in sepsis is enhanced by the depletion of antioxidants and scavenger enzymes such as glutathione and thiamine in the plasma<sup>[56,58]</sup>. Several studies have suggested that the oxidative stress can induce pancreatic damage in septic shock<sup>[32,59]</sup>.

**Triglycerides:** Serum triglyceride level has been reported to be significantly increased in septic shock<sup>[60,61]</sup>. Moreover, compared to those patients who survived septic shock, patients who died from it have been found to have a higher serum triglyceride level over the first 7 d of their illness<sup>[62]</sup>. Whether the high level of serum triglyceride seen in patients with septic shock is enough to induce pancreatic cell damage need to be investigated.

## CLINICAL RELEVANCE OF PANCREATIC INJURY

The clinical relevance of increased amylase and/or lipase in patient with septic shock has been poorly investigated. Whether pancreatic injury is only a satellite phenomenon or a major condition affecting the prognosis of this group of patients is still a matter of debate. In fact, only a few studies, most of them with a small number of patients, have investigated pancreatic dysfunction in critically-

ill patients<sup>[19,21,23-25,44]</sup>. Pezzilli *et al.*<sup>[23]</sup> have reported that amylase and lipase levels are significantly increased in patients with septic shock in comparison to a control group. However, none of the included patients met the criteria of acute pancreatitis and no significant correlation was found with mortality. These findings have been corroborated by post-mortem pancreatic tissue sample examination which has not shown significant morphological changes<sup>[24]</sup>.

Available data suggest that imaging tests should not be requested for all critically-ill patients with deranged pancreatic enzymes as long as the clinical assessment does not suggest acute pancreatitis. In fact, Denz *et al.*<sup>[19]</sup> reported that contrast enhanced computed tomography performed for all patients with a serum lipase level higher than 450 U/L was positive only in 35% of the patients. None of these patients had severe necrotizing pancreatitis which required specific management. However, the authors have reported that imaging abnormalities are more common in patients with increased blood levels of pancreatitis-associated protein. This raises the question: Which marker can be considered as a reliable test to assess the pancreatic dysfunction?

Even though the available data shows that the increase in the levels of pancreatic enzymes does not affect the mortality in critically-ill patients, the pancreatic dysfunction may cause malnutrition in patient with prolonged stay in intensive care units. In fact, the pancreatic secretory function is important for the digestion and absorption of fats, protein and carbohydrates<sup>[63]</sup>. In a prospective cross-sectional study of 563 critically-ill patients, Wang *et al.*<sup>[64]</sup> reported that the prevalence of exocrine pancreatic insufficiency in these patients is 52.2% although only 34.9% of these patients had increased serum lipase levels and only 30.2% had increased serum amylase levels. The definition of exocrine pancreatic insufficiency in their study was based on decreased fecal elastase-1 concentration (< 200 mcg/g). The authors have also found that both shock and sepsis are independent factors which predict exocrine pancreatic insufficiency. Tribi *et al.*<sup>[25]</sup> have reported similar results as they found that the concentration of amylase and chymotrypsin in the duodenal juice is significantly lower in patients with sepsis or septic shock than in healthy volunteers. Moreover, the concentration of trypsin is significantly lower in septic shock patients than sepsis patients without shock. The therapeutic implications of these findings need to be investigated by further studies.

## CONCLUSION

Pancreatic injury is common in patients suffering from septic shock. Increase in levels of pancreatic enzymes does not significantly affect the outcome. Only those patients who show clinical features of acute pancreatitis need to undergo further radiological investigations. However, pancreatic dysfunction may affect the nutritional state of patients receiving enteral feeding and requiring prolonged ICU stay. Whether specific treatment should be considered to avoid malnutrition in these patients need to

be investigated further.

## REFERENCES

- Dellinger RP**, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; **36**: 296-327 [PMID: 18158437 DOI: 10.1007/s00134-007-0934-2]
- Angus DC**, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29**: 1303-1310 [PMID: 11445675 DOI: 10.1097/0003246-200107000-00002]
- Martin GS**, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348**: 1546-1554 [PMID: 12700374 DOI: 10.1056/NEJMoa022139]
- Sasse KC**, Nauenberg E, Long A, Anton B, Tucker HJ, Hu TW. Long-term survival after intensive care unit admission with sepsis. *Crit Care Med* 1995; **23**: 1040-1047 [PMID: 7774214 DOI: 10.1097/00003246-199506000-00008]
- Annane D**, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: the CUB-Réa Network. *Am J Respir Crit Care Med* 2003; **168**: 165-172 [PMID: 12851245 DOI: 10.1164/rccm.2201087]
- Moemen ME**. Prognostic categorization of intensive care septic patients. *World J Crit Care Med* 2012; **1**: 67-79 [PMID: 24701404 DOI: 10.5492/wjccm.v1.i3.67]
- Leteurtre S**, Duhamel A, Deken V, Lacroix J, Leclerc F. Daily estimation of the severity of organ dysfunctions in critically ill children by using the PELOD-2 score. *Crit Care* 2015; **19**: 324 [PMID: 26369662 DOI: 10.1186/s13054-015-1054-y]
- Honore PM**, Jacobs R, Hendrickx I, Bagshaw SM, Joannes-Boyau O, Boer W, De Waele E, Van Gorp V, Spapen HD. Prevention and treatment of sepsis-induced acute kidney injury: an update. *Ann Intensive Care* 2015; **5**: 51 [PMID: 26690796 DOI: 10.1186/s13613-015-0095-3]
- Bagshaw SM**, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin J Am Soc Nephrol* 2007; **2**: 431-439 [PMID: 17699448 DOI: 10.2215/CJN.03681106]
- Gurjar M**, Baronia AK, Azim A, Prasad N, Jain S, Singh RK, Poddar B, Bhadauria D. Septic acute kidney injury in critically ill Indian patients. *Indian J Crit Care Med* 2013; **17**: 49-52 [PMID: 23833478 DOI: 10.4103/0972-5229.112147]
- Horvath T**, Trauner M, Fuhrmann V. Hypoxic liver injury and cholestasis in critically ill patients. *Curr Opin Crit Care* 2013; **19**: 128-132 [PMID: 23403733 DOI: 10.1097/MCC.0b013e32835ec9e6]
- Fuhrmann V**, Kneidinger N, Herkner H, Heinz G, Nikfardjam M, Bojic A, Schellongowski P, Angermayr B, Schöninger-Hekele M, Madl C, Schenk P. Impact of hypoxic hepatitis on mortality in the intensive care unit. *Intensive Care Med* 2011; **37**: 1302-1310 [PMID: 21647720 DOI: 10.1007/s00134-011-2248-7]
- Ji MH**, Yang JJ, Wu J, Li RQ, Li GM, Fan YX, Li WY. Experimental sepsis in pigs--effects of vasopressin on renal, hepatic, and intestinal dysfunction. *Ups J Med Sci* 2012; **117**: 257-263 [PMID: 22283426 DOI: 10.3109/03009734.2011.650796]
- Ljungdahl M**, Rasmussen I, Haglund U. Intestinal blood flow and intramucosal pH in experimental peritonitis. *Shock* 1999; **11**: 44-50 [PMID: 9921716 DOI: 10.1097/00024382-199901000-00007]
- Levy B**, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, Nabet P, Larcan A. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized



- study. *Intensive Care Med* 1997; **23**: 282-287 [PMID: 9083230 DOI: 10.1007/s001340050329]
- 16 **Rattner DW**, Gu ZY, Vlahakes GJ, Warshaw AL. Hyperamylasemia after cardiac surgery. Incidence, significance, and management. *Ann Surg* 1989; **209**: 279-283 [PMID: 2466447]
- 17 **Vitale GC**, Larson GM, Davidson PR, Bouwman DL, Weaver DW. Analysis of hyperamylasemia in patients with severe head injury. *J Surg Res* 1987; **43**: 226-233 [PMID: 2442498 DOI: 10.1016/0022-4804(87)90075-8]
- 18 **Weaver DW**, Busuito MJ, Bouwman DL, Wilson RF. Interpretation of serum amylase levels in the critically ill patient. *Crit Care Med* 1985; **13**: 532-533 [PMID: 2408820 DOI: 10.1097/00003246-198507000-00003]
- 19 **Denz C**, Siegel L, Lehmann KJ, Dagorn JC, Fiedler F. Is hyperlipasemia in critically ill patients of clinical importance? An observational CT study. *Intensive Care Med* 2007; **33**: 1633-1636 [PMID: 17497124 DOI: 10.1007/s00134-007-0668-1]
- 20 **Treacy J**, Williams A, Bais R, Willson K, Worthley C, Reece J, Bessell J, Thomas D. Evaluation of amylase and lipase in the diagnosis of acute pancreatitis. *ANZ J Surg* 2001; **71**: 577-582 [PMID: 11552931 DOI: 10.1046/j.1445-2197.2001.02220.x]
- 21 **Manjuck J**, Zein J, Carpati C, Astiz M. Clinical significance of increased lipase levels on admission to the ICU. *Chest* 2005; **127**: 246-250 [PMID: 15653991 DOI: 10.1378/chest.127.1.246]
- 22 **Working Group IAP/APA Acute Pancreatitis Guidelines**. IAP/ APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol* 2013; **13**: e1-15 [PMID: 24054878 DOI: 10.1016/j.pan.2013.07.063]
- 23 **Pezzilli R**, Barassi A, Imbrogno A, Fabbri D, Pigna A, Morselli-Labate AM, Corinaldesi R, Melzi d'Eril G. Is the pancreas affected in patients with septic shock?--a prospective study. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 191-195 [PMID: 21459727 DOI: 10.1016/S1499-3872(11)60030-1]
- 24 **Tribl B**, Madl C, Mazal PR, Schneider B, Spitzauer S, Vogelsang H, Gangl A. Exocrine pancreatic function in critically ill patients: septic shock versus non-septic patients. *Crit Care Med* 2000; **28**: 1393-1398 [PMID: 10834684 DOI: 10.1097/00003246-200005000-00022]
- 25 **Tribl B**, Sibbald WJ, Vogelsang H, Spitzauer S, Gangl A, Madl C. Exocrine pancreatic dysfunction in sepsis. *Eur J Clin Invest* 2003; **33**: 239-243 [PMID: 12641542 DOI: 10.1046/j.1365-2362.2003.01117.x]
- 26 **Raper RF**, Sibbald WJ, Hobson J, Rutledge FS. Effect of PGE1 on altered distribution of regional blood flows in hyperdynamic sepsis. *Chest* 1991; **100**: 1703-1711 [PMID: 1959417 DOI: 10.1378/chest.100.6.1703]
- 27 **Hiltebrand LB**, Krejci V, Banic A, Erni D, Wheatley AM, Sigurdsson GH. Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock. *Crit Care Med* 2000; **28**: 3233-3241 [PMID: 11008987 DOI: 10.1097/00003246-20000900-00019]
- 28 **Laine VJ**, Nyman KM, Peuravuori HJ, Henriksen K, Parvonen M, Nevalainen TJ. Lipopolysaccharide induced apoptosis of rat pancreatic acinar cells. *Gut* 1996; **38**: 747-752 [PMID: 8707123 DOI: 10.1136/gut.38.5.747]
- 29 **Kimura K**, Shimosegawa T, Abe R, Masamune A, Satoh A, Takasu A, Koizumi M, Toyota T. Low doses of lipopolysaccharide upregulate acinar cell apoptosis in cerulein pancreatitis. *Pancreas* 1998; **17**: 120-126 [PMID: 9700941 DOI: 10.1097/00006676-199808000-00002]
- 30 **Ruetten H**, Southan GJ, Abate A, Thiemermann C. Attenuation of endotoxin-induced multiple organ dysfunction by 1-amino-2-hydroxy-guanidine, a potent inhibitor of inducible nitric oxide synthase. *Br J Pharmacol* 1996; **118**: 261-270 [PMID: 8735625 DOI: 10.1111/j.1476-5381.1996.tb15397.x]
- 31 **Emanuelli G**, Montruccio G, Dughera L, Gaia E, Lupia E, Battaglia E, De Martino A, De Giuli P, Gubetta L, Camussi G. Role of platelet activating factor in acute pancreatitis induced by lipopolysaccharides in rabbits. *Eur J Pharmacol* 1994; **261**: 265-272 [PMID: 7813547 DOI: 10.1016/0014-2999(94)90116-3]
- 32 **Sakorafas GH**, Tsiotos GG, Sarr MG. Ischemia/Reperfusion-Induced pancreatitis. *Dig Surg* 2000; **17**: 3-14 [PMID: 10720825 DOI: 10.1159/000018793]
- 33 **Steinberg W**, Tenner S. Acute pancreatitis. *N Engl J Med* 1994; **330**: 1198-1210 [PMID: 7811319 DOI: 10.1056/NEJM199404283301706]
- 34 **Angus DC**, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013; **369**: 2063 [PMID: 24256390 DOI: 10.1056/NEJMra1208623]
- 35 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: 23361625 DOI: 10.1007/s00134-012-2769-8]
- 36 **Grum CM**. Tissue oxygenation in low flow states and during hypoxemia. *Crit Care Med* 1993; **21**: S44-S49 [PMID: 8428497 DOI: 10.1097/00003246-199302001-00009]
- 37 **Spormann H**, Sokolowski A, Letko G. Effect of temporary ischemia upon development and histological patterns of acute pancreatitis in the rat. *Pathol Res Pract* 1989; **184**: 507-513 [PMID: 2748464 DOI: 10.1016/S0344-0338(89)80143-8]
- 38 **Zhou ZG**, Chen YD. Influencing factors of pancreatic micro-circulatory impairment in acute pancreatitis. *World J Gastroenterol* 2002; **8**: 406-412 [PMID: 12046059 DOI: 10.3748/wjg.v8.i3.406]
- 39 **Levi M**, van der Poll T. Inflammation and coagulation. *Crit Care Med* 2010; **38**: S26-S34 [PMID: 20083910 DOI: 10.1097/CCM.0b013e3181c98d21]
- 40 **Levi M**, Schultz M, van der Poll T. Disseminated intravascular coagulation in infectious disease. *Semin Thromb Hemost* 2010; **36**: 367-377 [PMID: 20614389 DOI: 10.1055/s-0030-1254046]
- 41 **Kojima M**, Shimamura K, Mori N, Oka K, Nakazawa M. A histological study on microthrombi in autopsy cases of DIC. *Bibl Haematol* 1983; **(49)**: 95-106 [PMID: 6421274 DOI: 10.1159/000408450]
- 42 **Ferkau A**, Gillmann HJ, Mischke R, Calmer S, Ecklebe S, Abid M, Minde JW, Echtermeyer F, Theilmeier G. Infection-associated platelet dysfunction of canine platelets detected in a flow chamber model. *BMC Vet Res* 2013; **9**: 112 [PMID: 23758817 DOI: 10.1186/1746-6148-9-112]
- 43 **Rauch U**, Bonderman D, Bohrmann B, Badimon JJ, Himer J, Riederer MA, Nemerson Y. Transfer of tissue factor from leukocytes to platelets is mediated by CD15 and tissue factor. *Blood* 2000; **96**: 170-175 [PMID: 10891447]
- 44 **Tribl B**, Bateman RM, Milkovich S, Sibbald WJ, Ellis CG. Effect of nitric oxide on capillary hemodynamics and cell injury in the pancreas during Pseudomonas pneumonia-induced sepsis. *Am J Physiol Heart Circ Physiol* 2004; **286**: H340-H345 [PMID: 12969889 DOI: 10.1152/ajpheart.00234.2003]
- 45 **Dhainaut JF**, Yan SB, Joyce DE, Pettit V, Basson B, Brandt JT, Sundin DP, Levi M. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost* 2004; **2**: 1924-1933 [PMID: 15550023 DOI: 10.1111/j.1538-7836.2004.00955.x]
- 46 **Simmons J**, Pittet JF. The coagulopathy of acute sepsis. *Curr Opin Anaesthesiol* 2015; **28**: 227-236 [PMID: 25590467 DOI: 10.1097/ACO.000000000000163]
- 47 **Bai X**, Yu W, Ji W, Lin Z, Tan S, Duan K, Dong Y, Xu L, Li N. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care* 2014; **18**: 532 [PMID: 25277635 DOI: 10.1186/s13054-014-0532-y]
- 48 **Rivers E**, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368-1377 [PMID: 11794169 DOI: 10.1056/NEJMoa010307]
- 49 **Rossaint J**, Zarbock A. Pathogenesis of Multiple Organ Failure in Sepsis. *Crit Rev Immunol* 2015; **35**: 277-291 [PMID: 26757392 DOI: 10.1615/CritRevImmunol.2015015461]
- 50 **Kim SM**, Sakai T, Dang HV, Tran NH, Ono K, Ishimura K, Fukui K. Nucling, a novel protein associated with NF- $\kappa$ B, regulates

- endotoxin-induced apoptosis in vivo. *J Biochem* 2013; **153**: 93-101 [PMID: 23071121 DOI: 10.1093/jb/mvs119]
- 51 **Roger PM**, Hyvern H, Ticchioni M, Kumar G, Dellamonica J, Bernardin G. The early phase of human sepsis is characterized by a combination of apoptosis and proliferation of T cells. *J Crit Care* 2012; **27**: 384-393 [PMID: 22824083 DOI: 10.1016/j.jcrc.2012.04.010]
  - 52 **Li YY**, Lu S, Li K, Feng JY, Li YN, Gao ZR, Chen CJ. Down-regulation of HSP60 expression by RNAi increases lipopolysaccharide- and cerulein-induced damages on isolated rat pancreatic tissues. *Cell Stress Chaperones* 2010; **15**: 965-975 [PMID: 20574674 DOI: 10.1007/s12192-010-0207-9]
  - 53 **Wang XL**, Li Y, Kuang JS, Zhao Y, Liu P. Increased heat shock protein 70 expression in the pancreas of rats with endotoxic shock. *World J Gastroenterol* 2006; **12**: 780-783 [PMID: 16521195 DOI: 10.3748/wjg.v12.i5.780]
  - 54 **Hotchkiss RS**, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, Buchman TG, Karl IE. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med* 1999; **27**: 1230-1251 [PMID: 10446814 DOI: 10.1097/00003246-199907000-00002]
  - 55 **Crimi E**, Sica V, Slutsky AS, Zhang H, Williams-Ignarro S, Ignarro LJ, Napoli C. Role of oxidative stress in experimental sepsis and multisystem organ dysfunction. *Free Radic Res* 2006; **40**: 665-672 [PMID: 16983993 DOI: 10.1080/10715760600669612]
  - 56 **Costa NA**, Gut AL, de Souza Dorna M, Pimentel JA, Cozzolino SM, Azevedo PS, Fernandes AA, Zornoff LA, de Paiva SA, Minicucci MF. Serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock. *J Crit Care* 2014; **29**: 249-252 [PMID: 24412011 DOI: 10.1016/j.jcrc.2013.12.004]
  - 57 **Oldham KM**, Bowen PE. Oxidative stress in critical care: is anti-oxidant supplementation beneficial? *J Am Diet Assoc* 1998; **98**: 1001-1008 [PMID: 9739800 DOI: 10.1016/S0002-8223(98)00230-2]
  - 58 **Huet O**, Cherreau C, Nicco C, Dupic L, Conti M, Borderie D, Pene F, Vicaute E, Benhamou D, Mira JP, Duranteau J, Batteux F. Pivotal role of glutathione depletion in plasma-induced endothelial oxidative stress during sepsis. *Crit Care Med* 2008; **36**: 2328-2334 [PMID: 18664787 DOI: 10.1097/CCM.0b013e3181800387]
  - 59 **Wray GM**, Hinds CJ, Thiemeermann C. Effects of inhibitors of poly(ADP-ribose) synthetase activity on hypotension and multiple organ dysfunction caused by endotoxin. *Shock* 1998; **10**: 13-19 [PMID: 9688085 DOI: 10.1097/00024382-199807000-00003]
  - 60 **Wendel M**, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II. Clinical aspects. *Intensive Care Med* 2007; **33**: 25-35 [PMID: 17093984 DOI: 10.1007/s00134-006-0433-x]
  - 61 **Murch O**, Collin M, Hinds CJ, Thiemeermann C. Lipoproteins in inflammation and sepsis. I. Basic science. *Intensive Care Med* 2007; **33**: 13-24 [PMID: 17093985 DOI: 10.1007/s00134-006-0432-y]
  - 62 **Lee SH**, Park MS, Park BH, Jung WJ, Lee IS, Kim SY, Kim EY, Jung JY, Kang YA, Kim YS, Kim SK, Chang J, Chung KS. Prognostic Implications of Serum Lipid Metabolism over Time during Sepsis. *Biomed Res Int* 2015; **2015**: 789298 [PMID: 26351639 DOI: 10.1155/2015/789298]
  - 63 **Domínguez-Muñoz JE**. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011; **26** Suppl 2: 12-16 [PMID: 21323992 DOI: 10.1111/j.1440-1746.2010.06600.x]
  - 64 **Wang S**, Ma L, Zhuang Y, Jiang B, Zhang X. Screening and risk factors of exocrine pancreatic insufficiency in critically ill adult patients receiving enteral nutrition. *Crit Care* 2013; **17**: R171 [PMID: 23924602 DOI: 10.1186/cc12850]

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Basic Study

## MicroRNA-320 family is downregulated in colorectal adenoma and affects tumor proliferation by targeting CDK6

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### Abstract

**AIM:** To investigate the microRNA (miRNA) expression during histological progression from colorectal normal mucosa through adenoma to carcinoma within a lesion.

**METHODS:** Using microarray, the sequential changes in miRNA expression profiles were compared in colonic lesions from matched samples; histologically, non-neoplastic mucosa, adenoma, and submucosal invasive carcinoma were microdissected from a tissue sample. Cell proliferation assay was performed to observe the effect of miRNA, and its target genes were predicted using bioinformatics approaches and the expression profile of SW480 transfected with the miRNA mimics. mRNA and protein levels of the target gene in colon cancer cell lines with a mimic control or miRNA mimics were measured using qRT-PCR and Western blotting. The expression levels of miRNA and target gene in colorectal tissue samples were also measured.

**RESULTS:** Microarray analysis identified that the miR-320 family, including miR-320a, miR-320b, miR-320c, miR-320d and miR-320e, were differentially expressed in adenoma

and submucosal invasive carcinoma. The miR-320 family, which inhibits cell proliferation, is frequently downregulated in colorectal adenoma and submucosal invasive carcinoma tissues. Seven genes including CDK6 were identified to be common in the results of gene expression array and bioinformatics analyses performed to find the target gene of the miR-320 family. We confirmed that mRNA and protein levels of CDK6 were significantly suppressed in colon cancer cell lines with miR-320 family mimics. CDK6 expression was found to increase from non-neoplastic mucosa through adenoma to submucosal invasive carcinoma tissues and showed an inverse correlation with miR-320 family expression.

**CONCLUSION:** MiR-320 family affects colorectal tumor proliferation by targeting CDK6, plays important role in its growth, and is considered to be a biomarker for its early detection.

**Key words:** CDK6; Colorectal cancer; MiR-320 family; Colorectal adenoma; Laterally spreading type

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**Core tip:** We investigated for the first time the sequential changes of miRNA expression profiles in colonic lesions from matched samples; histologically, non-neoplastic mucosa, adenoma, and submucosal invasive carcinoma were microdissected from a tissue sample. We have shown that the miR-320a, miR-320b, miR-320c, miR-320d are downregulated from colorectal adenoma and miR-320e is downregulated from colorectal submucosal carcinoma tissue and the miR-320 family suppresses tumor proliferation by targeting CDK6. The miR-320 family may play an important role in the growth of colorectal tumors and can be considered as a biomarker for the early detection of colorectal tumors.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies resulting in cancer-related deaths in the world<sup>[1]</sup>. The adenoma-carcinoma sequence, which involves a series of changes from normal colorectal epithelium through an adenoma to an invasive and metastatic tumor, has been widely recognized as an important developmental mechanism in CRC<sup>[2]</sup>. According to this theory, the colorectal adenoma (CRA) is considered

to be a precursor lesion of CRC; the removal of CRAs by polypectomy has been shown to reduce the incidence and mortality due to CRCs<sup>[3]</sup>. Endoscopic mucosal resection and endoscopic submucosal dissection (ESD) enable resection of almost all intramucosal neoplasia with submucosal invasion of less than 1000  $\mu$ m in the colon<sup>[4]</sup>. Thus, detection of colorectal tumors in the early stages has become increasingly important in treatment and prognosis.

The adenoma-carcinoma sequence is accompanied by several genetic and epigenetic alterations, such as mutations of cancer-associated genes and epigenetic modifications, including changes in DNA methylation, histone modifications, and microRNAs (miRNAs)<sup>[5,6]</sup>. However, the involvement of miRNAs in the mechanism of this sequence remains undetermined. miRNAs are small (19-23 nucleotide) endogenous non-coding RNAs that regulate gene expression by targeting the 3' untranslated region (UTR) of mRNA. miRNAs play fundamental roles in various biological processes<sup>[7]</sup>. Accumulating evidence indicates that miRNAs are frequently dysregulated in human cancers<sup>[8]</sup>, and alterations of miRNA expression in colorectal tumors have been well documented. For example, miRNA profiles of CRC compared with those of normal mucosa<sup>[9]</sup> and adenoma<sup>[6,10]</sup> have been reported. However, limited reports exist on the sequential changes in miRNA expression during histological progression from normal colonic mucosa through colorectal adenoma to early carcinoma in a lesion from a patient.

Furthermore, according to the Paris and Japanese classification<sup>[11,12]</sup>, a flat colorectal lesion exceeding 10 mm in diameter is classified as a "laterally spreading type (LST)" and subclassified into a granular (G) or a non-granular (NG) type. The percentage of gene mutation in the protruded tumor is hypothesized to be different from that of the LST<sup>[13]</sup>. When we focused on miRNA, expression changes of some miRNAs in exophytic and flat elevated tumors were reported<sup>[14]</sup>; however, there is no analysis comparing miRNA expressions of the LST with those of the protruded tumor.

Therefore, we analyzed miRNA expressions of both LSTs and protruded tumors as a specific feature of the stepwise progression from adjacent non-neoplastic mucosa to adenoma and submucosal invasive carcinoma using matched samples to compare accurate miRNA expression in each phase.

## MATERIALS AND METHODS

### Tissue samples

Formalin-fixed, paraffin-embedded (FFPE) colorectal tissue samples that included carcinoma, adenoma, and adjacent non-neoplastic mucosa were obtained from patients who underwent ESD at Tohoku University between January 2011 and December 2014 and provided written informed consent for study participation. All the cancers were limited to submucosal carcinomas, which were classified as T1MON0 (American Joint Committee on Cancer Staging

Manual) in this study. The 18 colorectal samples were LST (15 carcinoma with adenoma and 3 carcinoma without adenoma) and the 3 colorectal samples were protruded-type carcinoma with adenoma.

A senior pathologist reviewed the histopathological grades and types of all cases. Regions of colorectal carcinoma, pre-existing adenoma, and adjacent non-neoplastic mucosa in a resection specimen were microdissected using a laser microdissection (LMD) system (Leica Microsystems, Wetzlar, Germany). This study was reviewed and approved by the ethics committee and the institutional review board at the Tohoku University Hospital.

### Cell lines and transfection

Human colon cancer cell lines HT29 and SW480 were obtained from the American Type Culture Collection (Manassas, VA) and then grown in Dulbecco's Modified Eagle's Medium supplemented with 10% (v/v) fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub>. The human intestinal epithelial cells (InEpC) were obtained from Lonza, Japan.

We used mirVana™ miRNA 320a, b, c, d, and e mimic; mimic control; inhibitor; and inhibitor control (Life Technologies, Carlsbad, CA). These RNA oligonucleotides were transiently transfected into SW480 and HT29 cells using the Lipofectamine RNAiMAX Reagent (Invitrogen, United States) according to the manufacturer's instructions.

### RNA isolation

Total RNA from microdissected FFPE samples was purified using a miRNAeasy FFPE kit (QIAGEN, Hilden, Germany). Total RNA isolated from cultured cells using TRIzol reagent (Invitrogen) was purified with an RNeasy Mini kit (QIAGEN).

### miRNA microarray analysis

The RNA from FFPE samples was labeled with a miRNA complete labeling and Hyb kit (Agilent Technologies, Santa Clara, CA, United States), and the labeled probes were hybridized onto Agilent Human miRNA Microarray Rel 19.0 according to the manufacturer's instructions. The arrays were scanned and the data were extracted and analyzed using the Agilent Feature Extraction software and Agilent GeneSpring software.

### Quantitative real-time polymerase chain reaction

RNA samples were reverse transcribed into cDNA using QuantiTect Reverse Transcription Kit and miScript II RT Kit (QIAGEN). Each cDNA sample was analyzed in triplicate using the QuantiFast SYBR Green PCR kit (QIAGEN) with the StepOnePlus real-time PCR system (Life Technologies). A comparative  $\Delta\Delta C_t$  method was used for the quantification of the miR-320 family and CDK6 expression; expression levels of the hsa-miR-320 family and CDK6 were normalized by those of U6 and GAPDH, respectively. A miScript Primer Assay (QIAGEN) was used for the miR-320 family and U6. The following primer sets were used for other quantitative reverse transcription (qRT)-PCR assays:

CDK6 Forward: 5'-GGATAAAGTTCCAGAGCCTGGAG-3';  
CDK6 Reverse: 5'-GCGATGCACTACTCGGTGTGAA-3';  
and GAPDH Forward: 5'-ATCAGCAATGCCTCCTGCAC-3';  
Reverse: 5'-ATGGCATGGACTGTGGTCAT-3'.

### Cell proliferation assay

Human colon cancer cell lines SW480 were seeded in 96-well plates, and cell proliferation was measured 24, 48, 72, 96, and 120 h later using the CellTiter96 Aqueous One Solution Cell Proliferation Assay (MTS assay; Promega, Madison, WI, United States) according to manufacturer's instructions.

### Gene expression analysis and miRNA target prediction

Gene expression profiling of SW480 transfected with a mimic control or miR-320a mimics was performed using the SurePrint G 3 Human Gene Expression 8x60K v2 Microarray Kit (Agilent Technologies) according to the manufacturer's instructions. Candidates of miRNA target genes were selected according to the results of these mRNA expression analysis and two different bioinformatics algorithms-TargetScan (<http://www.targetscan.org>) and Pic tar (<http://pictar.mdc-berlin.de/>).

### Protein extraction and Western blot

Total cell lysates were prepared using a mammalian cell extraction kit (BioVision, Mountain View, CA, United States). Protein concentrations in the lysates were measured using the BCA Protein Assay kit (Pierce Chemical Co., Rockford, IL, United States). Equal amounts of proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride membranes. After incubation with Tris-buffered saline and Tween-20 containing an ECL blocking agent, the membranes were incubated with primary antibodies against CDK6 (Cell Signaling Technology, Inc., Danvers, MA, United States) or  $\alpha$ -tubulin (B512, Sigma) at 4 °C overnight and further incubated with secondary antibodies for 1 h at room temperature. Reactive bands were detected using the ECL Prime Western Blotting Detection Reagent (GE Healthcare, Bucks, United Kingdom).

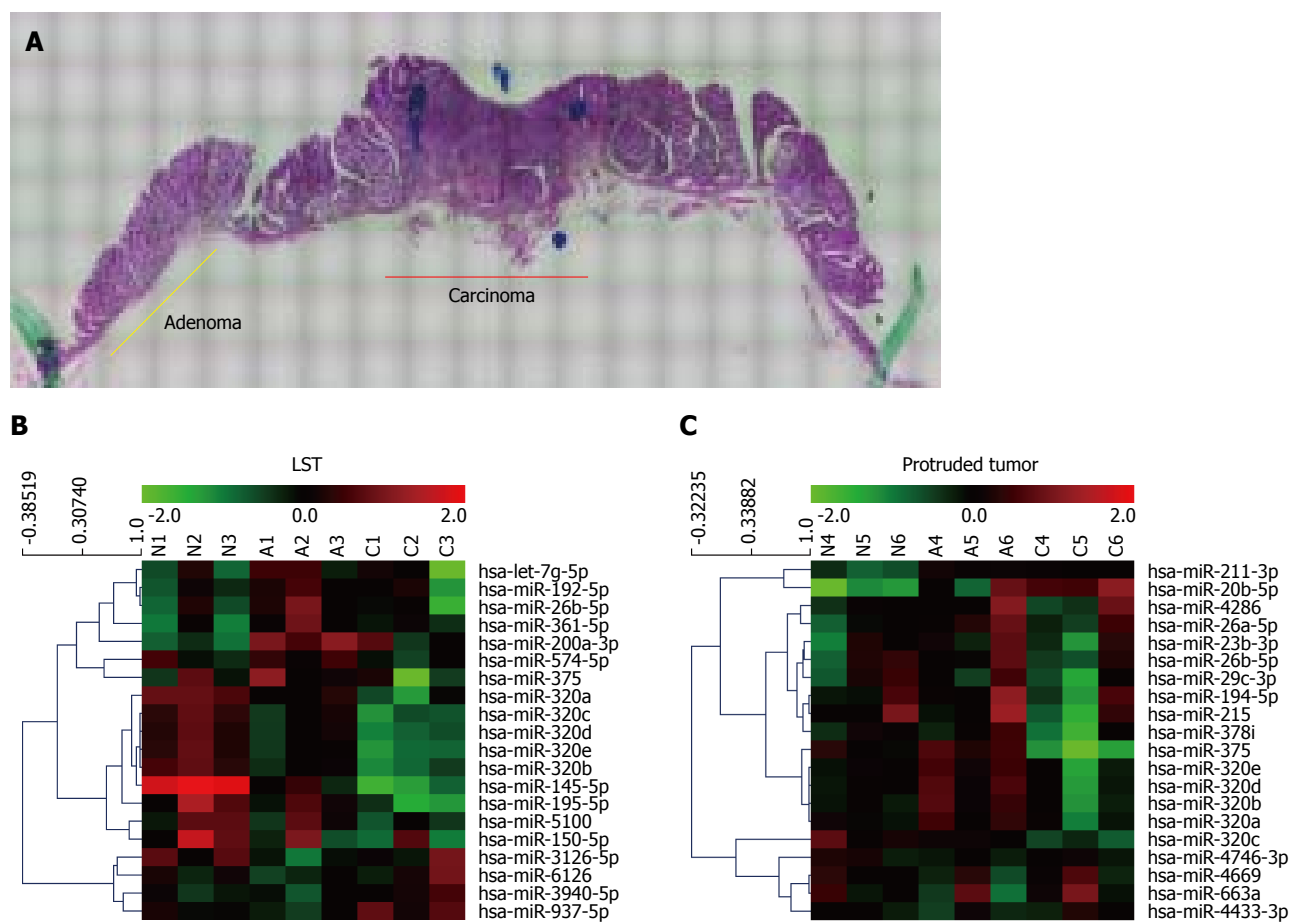
### Statistical analysis

Data from at least three independent experiments were analyzed. Statistical analysis was conducted using Excel (Microsoft). The difference between two groups was analyzed using the paired *t*-test for miRNA array data and the Student's *t*-test for qRT-PCR data. The statistical significance of correlations between the expressions of the miR-320 family and CDK6 mRNA was evaluated using Pearson's correlation analysis. *P* < 0.05 was considered statistically significant.

## RESULTS

### Most miRNAs associated with the adenoma-carcinoma sequence were common to LSTs and protruded tumors

Sequential changes of miRNA expression profiles from matched samples, histologically non-neoplastic mu-



**Figure 1** MiRNA expression profiles of matched samples. A: Regions of colorectal carcinoma, pre-existing adenoma, and adjacent non-neoplastic mucosa in a resection specimen were microdissected using laser microdissection (LMD); B and C: The miRNA expression profiles were compared with three matched regions from LSTs ( $n = 3$ ) and protruded tumors ( $n = 3$ ). For each miRNA, red represents higher expression and green represents lower expression than the average expression. LST: Laterally spreading type; C: Carcinoma; A: Adenoma; N: Adjacent non-neoplastic mucosa.

cosa, adenoma, and submucosal invasive carcinoma microdissected by LMD from a tissue sample (Figure 1A), were assessed. To differentiate tumor forms, these analyses were conducted in each of the LSTs ( $n = 3$ ) and protruded tumors ( $n = 3$ ) (Figure 1B and C). All three LSTs were of the granular type. Seven miRNAs in LSTs and 23 miRNAs in protruded tumors showed significantly higher or lower expression in early carcinomas than that in adenomas, with expression in non-neoplastic mucosa as the baseline. The top 10 miRNAs in each form are summarized in Table 1. Comparing these results, six of the 10 miRNAs, including five belonging to the miR-320 family (320a, b, c, d, and e) were identical. In addition, we confirmed the downregulation of miR-195 (LST), miR-375, miR-378 (protruded tumor), and miR-26b (both forms) in early cancer, which has been previously reported in several studies of CRCs<sup>[9,15,16]</sup>. Decreased expression of miR-320a and 320b in CRC has also been reported previously<sup>[6,17,18]</sup>. It is interesting that these changes in miR-320 family expressions are common in early carcinomas both in LSTs and protruded tumors; therefore, we focused on

the miR-320 family in the subsequent analysis.

#### **miR-320 family is significantly downregulated in colorectal adenoma and submucosal invasive carcinoma**

To confirm the downregulation of the miR-320 family in early carcinoma, we conducted qRT-PCR of the miR-320 family using 18 matched colorectal submucosal invasive carcinoma specimens in LSTs (Figure 2A). Expressions of all members of the miR-320 family except miR-320e in adenoma were significantly decreased not only in submucosal invasive carcinomas but also in adenomas compared with those in the non-neoplastic mucosa ( $P < 0.05$  and  $P < 0.01$ , respectively). On comparing adenomas and carcinomas, expression levels of the miR-320 family, except for 320d, in carcinomas were lower than that in adenomas; however, differences were not statistically significant. These findings were confirmed in human colon cancers cell lines by qRT-PCR, and expression of the miR-320 family was found to be decreased in HT29 and SW480 compared with that in InEpc (Figure 2B).

These results indicated that the expression of the miR-320 family decreased from the early stages of the



**Table 1 The top 10 miRNA changes between colorectal adenoma and carcinoma**

	Systematic name	Expression levels <i>vs</i> normal (mean $\pm$ SD)		<i>P</i> value
		Adenoma	Carcinoma	
Laterally spreading types ( <i>n</i> = 3)				
1	hsa-miR-320b	0.649 $\pm$ 0.170	0.402 $\pm$ 0.146	0.00488
2	hsa-miR-320e	0.666 $\pm$ 0.159	0.376 $\pm$ 0.085	0.0213
3	hsa-miR-937-5p	0.842 $\pm$ 0.169	1.446 $\pm$ 0.253	0.0215
4	hsa-miR-574-5p	1.287 $\pm$ 0.477	0.881 $\pm$ 0.339	0.0373
5	hsa-miR-320d	0.705 $\pm$ 0.204	0.425 $\pm$ 0.108	0.0407
6	hsa-miR-320a	0.645 $\pm$ 0.140	0.412 $\pm$ 0.198	0.0417
7	hsa-miR-26b-5p	1.751 $\pm$ 0.307	1.003 $\pm$ 0.600	0.0477
8	hsa-miR-320c	0.676 $\pm$ 0.181	0.401 $\pm$ 0.072	0.0516
9	hsa-miR-361-5p	1.976 $\pm$ 0.124	1.469 $\pm$ 0.378	0.0762
10	hsa-miR-195-5p	0.729 $\pm$ 0.172	0.391 $\pm$ 0.338	0.0772
Protruded tumors ( <i>n</i> = 3)				
1	hsa-miR-320d	1.450 $\pm$ 0.388	0.805 $\pm$ 0.369	0.000284
2	hsa-miR-320b	1.456 $\pm$ 0.386	0.834 $\pm$ 0.362	0.00203
3	hsa-miR-375	1.312 $\pm$ 0.163	0.285 $\pm$ 0.174	0.00492
4	hsa-miR-320e	1.350 $\pm$ 0.278	0.772 $\pm$ 0.362	0.00724
5	hsa-miR-320c	0.879 $\pm$ 0.236	0.584 $\pm$ 0.219	0.0105
6	hsa-miR-320a	1.262 $\pm$ 0.208	0.810 $\pm$ 0.263	0.0110
7	hsa-miR-663a	0.985 $\pm$ 0.786	1.317 $\pm$ 0.798	0.0114
8	hsa-miR-211-3p	1.634 $\pm$ 0.193	1.533 $\pm$ 0.189	0.0129
9	hsa-miR-378i	1.110 $\pm$ 0.223	0.640 $\pm$ 0.333	0.0250
10	hsa-miR-26b-5p	1.261 $\pm$ 0.462	0.896 $\pm$ 0.360	0.0253

adenoma-carcinoma sequence.

#### **miR-320 family, except miR-320e, inhibits cell proliferation**

To reveal the role of the miR-320 family in CRC, cell proliferations in SW480 transfected with the miR-320 family were analyzed by MTS assay for 5 d. Overexpression of miR-320a, 320b, 320c, or 320d significantly inhibited the cell growth of SW480 (Figure 3), and inhibition of these miRNA significantly promoted proliferation of SW480 (data not shown). However, these findings were not observed with miR-320e.

#### **miR-320a targets CDK6**

To find a target gene of the miR-320 family, we used miR-320a as a representative of the miR-320 family in microarray gene expression analysis and miRNA target prediction. Before the gene expression analysis, we confirmed that the expression of miR-320a in SW480 cells transfected with miR-320a mimics was increased by approximately 1600-fold compared with that in controls. Next, the gene expression analysis of SW480 with a mimic control or miR-320a mimics was conducted using microarray, and the expressions of 497 genes were found to be decreased in SW480 with miR-320a mimics (fold-change < 0.67). In addition to these tests, we conducted TargetScan and Pic tar analyses to detect potential targets of miR-320a; seven genes (BLCAP, HOXA10, KCNS3, RASA1, NPAS2, ARPC5, and CDK6) were identified to be common in the results of these three different analyses (Figure 4A). In seven candidate genes, CDK6 expression was shown to be associated with prognosis in patients with CRC<sup>[19]</sup>; moreover, the results of miRNA binding-site prediction analyses using bioinformatics tools (Target scan

and microRNA.org) indicate that CDK6 has a putative miR-320 family's binding site that is mapped to the 3' UTR (Figure 4B). From these results, we selected CDK6 as a novel candidate target of the miR-320 family.

#### **mRNA and protein levels of CDK6 suppressed by miR-320 family in colon cancer cell lines**

To examine whether the miR-320 family influences both mRNA and protein levels of CDK6, these were analyzed in colon cancer cell lines (HT29 and SW480) with a mimic control or miR-320 family mimics. Both mRNA and protein levels of CDK6 were significantly suppressed in cells with miR-320 family mimics (Figure 4C and D).

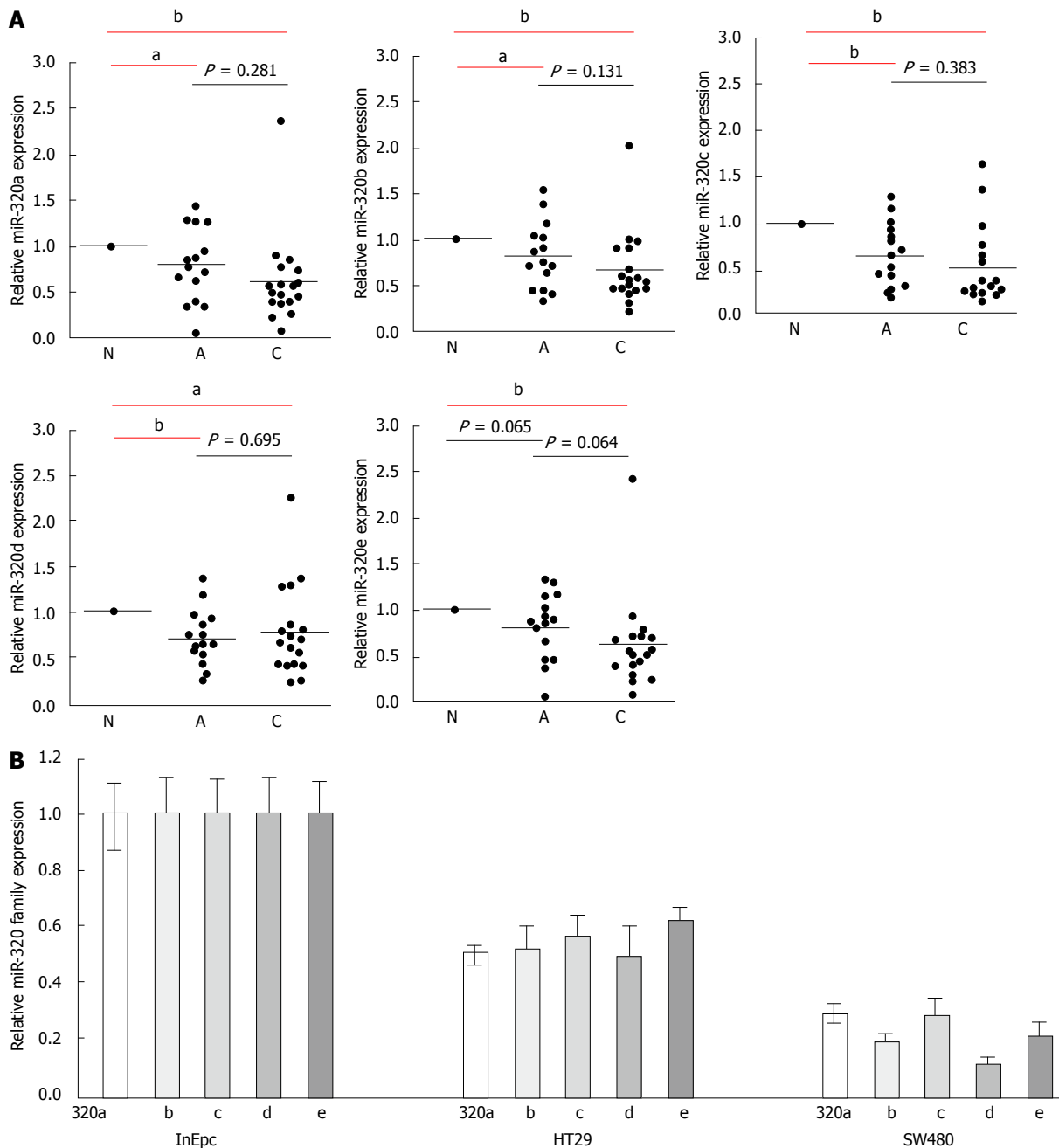
#### **Increased CDK6 expression from non-neoplastic mucosa through adenoma to submucosal invasive carcinoma with inverse correlation to the miR-320 family expression**

To confirm the changes of CDK6 expression in colorectal tissues, we investigated CDK6 expression in FFPE tissues of 18 matched samples. Two samples were excluded because of difficulty in detecting CDK6 expression. CDK6 expression in submucosal invasive carcinoma compared with non-neoplastic mucosa was significantly increased ( $P < 0.05$ , Figure 4E) and that in adenoma was also increased but without statistical significance ( $P = 0.10$ ). Finally, we found that there is an inverse correlation between the expression levels of the miR-320 family, except miR-320c, and CDK6 in the 16 matched samples studied ( $P < 0.05$ , Figure 4F).

## **DISCUSSION**

The main aim of this study was to investigate changes



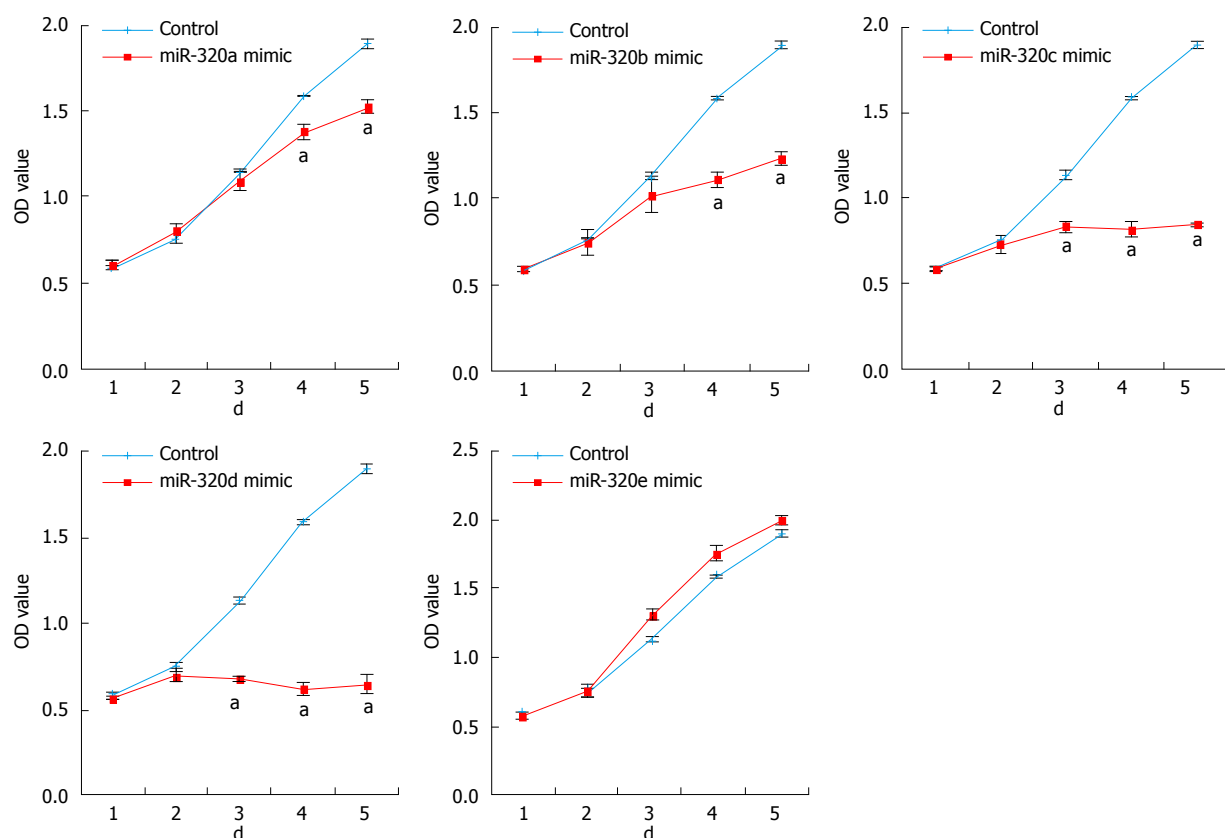


**Figure 2** The relative expression levels of the miR-320 family in formalin-fixed, paraffin-embedded samples and cell lines. A: The expression of the miR-320 family in 18 samples (15 colorectal carcinoma with adenoma and 3 colorectal carcinoma without adenoma); B: The expression of the miR-320 family in human colon cancers cell lines (HT29 and SW480) compared with that in human intestinal epithelial cells (InEpC). (<sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$ ). C: Carcinoma, A: Adenoma, N: Adjacent non-neoplastic mucosa.

in miRNAs corresponding to the adenoma-carcinoma sequence and to clarify the functions of these miRNAs in carcinogenesis. We showed that the miR-320 family (a, b, c, d and e) were important factors in the progression of the early stages of colorectal tumors and found a novel target of the miR-320 family, CDK6. From the results of our comprehensive microarray miRNA analysis, miR-320a, b, c, d and e were downregulated from adenoma to submucosal invasive carcinoma in both LSTs and protruded tumors. It has been previously reported that miR-320a regulates tumor occurrence<sup>[20]</sup>, progression<sup>[21]</sup>, and metastasis<sup>[22]</sup> in CRC; therefore, we inferred that the miR-320 family may play an important role in colo-

rectal carcinogenesis<sup>[23]</sup>. Moreover, 6 of the 10 miRNAs, including the miR-320 family, were identical between the LST-G type and protruded tumors; therefore, there is a possibility that the carcinogenic mechanisms of these two different forms share similar pathways. In contrast, the LST-NG type has been reported to show a significantly higher frequency of submucosal invasion than the LST-G type<sup>[24]</sup>; thus, their carcinogenic mechanisms might be different. Further verification of the carcinogenic mechanisms of the LST-NG type is warranted.

To investigate the expression of the miR-320 family in the colorectal tissue, we conducted expression analysis of the miR-320 family in 18 FFPE samples by RT-PCR.



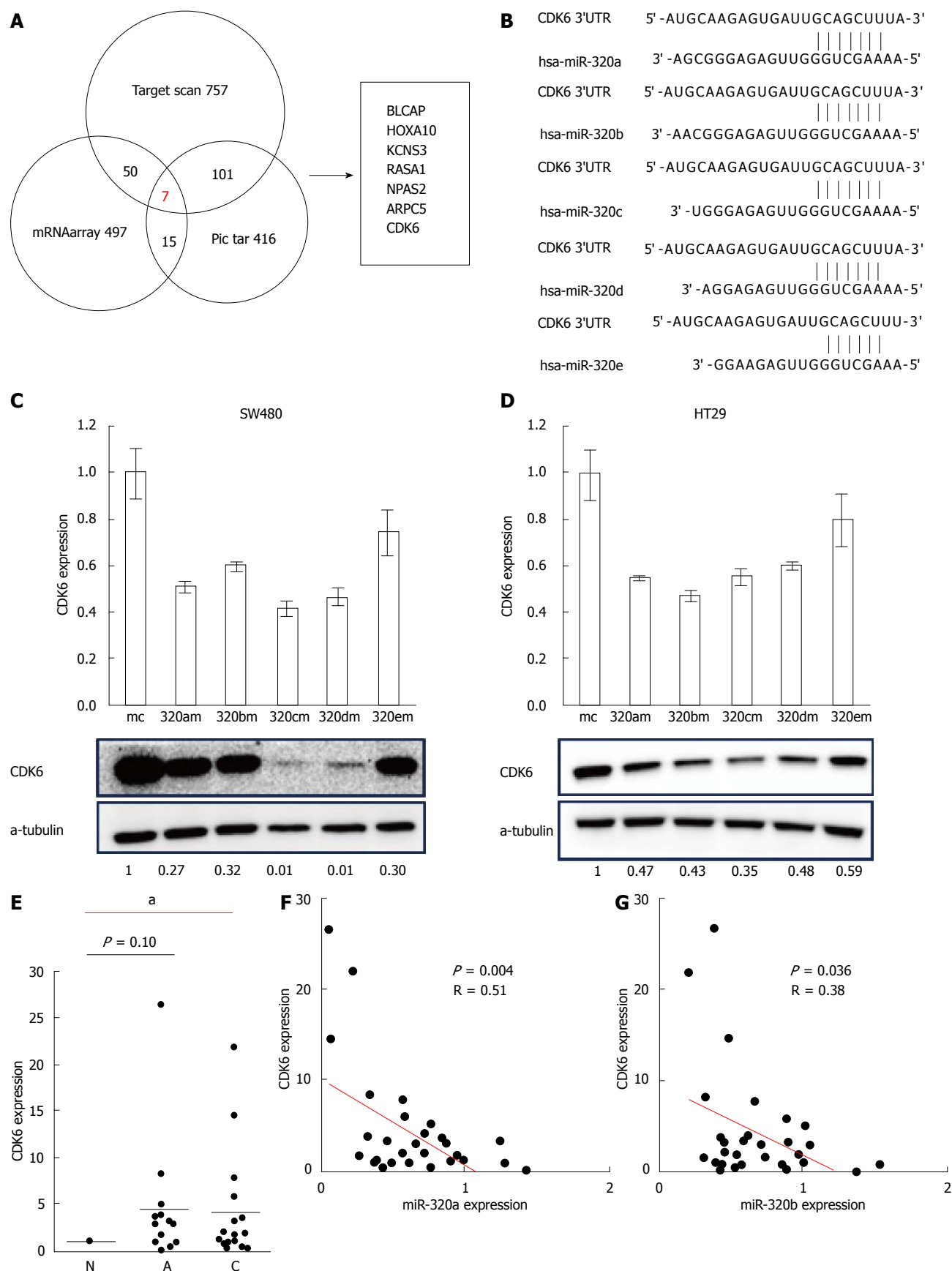
**Figure 3** The miR-320 family inhibits colon cancer cell proliferation. Cell proliferation in SW480 transfected with the miR-320 family was assessed by the MTS assay, each day, for up to 5 d ( $^aP < 0.05$ ).

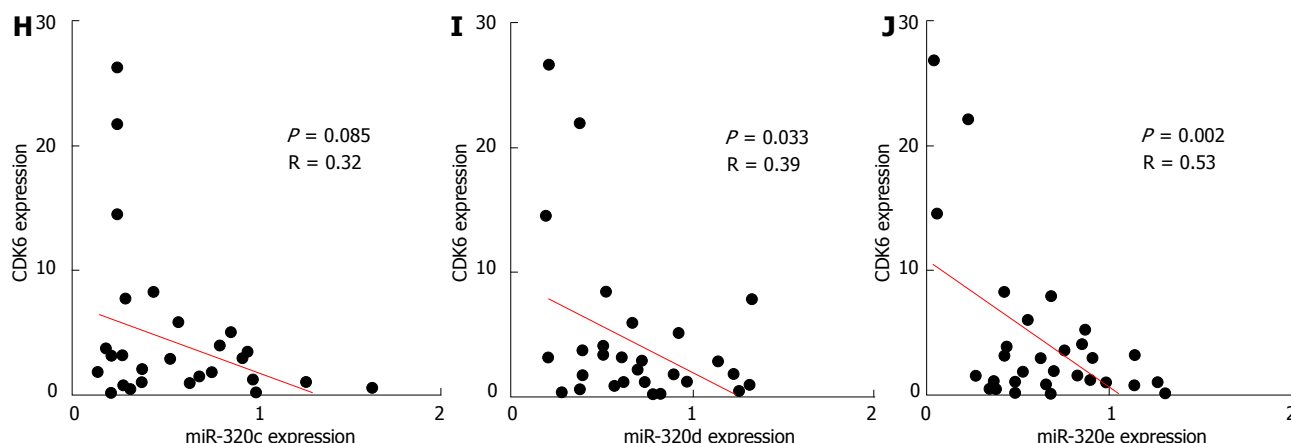
In addition to the results from our miRNA microarray analysis, which showed differences of the miR-320 expression between colorectal adenoma and carcinoma, qRT-PCR analyses showed progressively decreasing expression of the miR-320 family, except miR-320d, from non-neoplastic mucosa through adenoma to submucosal invasive carcinoma. There are some reports of a relationship between miRNA and colorectal adenoma<sup>[6,25]</sup>, and miR-320a was downregulated from colorectal mucosa to low-grade dysplasia to high-grade dysplasia to adenocarcinomas in the same sample<sup>[6]</sup>. Our results support these previous findings, and this article presents the first report of the downregulation of miR-320b in CRA, miR-320c and d in CRA and CRC, and miR-320e in CRC. miR-320a has been shown to effectively regulate proliferation, cell cycle, invasion, migration, and epithelial-mesenchymal transition of CRC, particularly in advanced stages, and is a novel tumor and metastasis suppressor acting by directly targeting mRNAs of neuropilin 1,  $\beta$ -catenin, and other genes<sup>[17]</sup>. We confirmed that miR-320a inhibited cell proliferation in cancer cell lines but not how it affects tumor progression in earlier stages of the tumor. Further, the carcinogenic mechanisms of miR-320b, c, d, and e are poorly understood, particularly in CRC. Therefore, we first tried to identify novel targets of the miR-320 family to identify the carcinogenic mechanism in the early stages of the adenoma-carcinoma sequence.

The most commonly used approach to find the target genes of miRNA is through bioinformatics algorithm. Recent reports have provided evidence that miRNAs may downregulate a greater number of transcripts than previously appreciated<sup>[26]</sup>; we adopted the results of the mRNA expression array analysis to narrow down the candidates. Finally, we selected seven target genes as common to two bioinformatics algorithms and our results of the mRNA array.

Carcinogenesis is believed to be caused by the dysregulation of the cell-cycle machinery. CDK6, a cyclin-D1-dependent kinase, plays an important role in G<sub>1</sub>/S phase transition of the cell cycle and sends signals modulating the control of cell development<sup>[27]</sup>. The function of CDK6 in CRC has been shown previously<sup>[19]</sup>, and there are several reports on the relationships between CDK6 and miRNA in some types of cancers<sup>[28]</sup>. Moreover, it was reported that miR-320c inhibited tumor-like behaviors of bladder cancer by targeting CDK6<sup>[29]</sup>. However, no studies have examined the relationship between the expression of the miR-320 family and CDK6 expression in CRC.

We confirmed the decreased expression of mRNA and CDK6 in CRC cell lines transfected with the miR-320 family. In addition, we confirmed that CDK6 expression was downregulated in colorectal tumor tissues and that the expressions levels of the miR-320 family, except miR-320c, were negatively correlated with the mRNA expression levels of CDK6. These results suggested that





**Figure 4** The miR-320 family targets CDK6. A: Seven candidate target genes of miR-320a were identified as being common from the results of expression profiling and two bioinformatics algorithms. The decreased expression of 497 pieces was observed in gene expression profiling of SW480 transfected with an miR-320a mimic and a mimic control (fold-change: < 0.67), and target genes of miR-320a were predicted by TargetScan and Pic tar; B: CDK6 has a putative miR-320 family-binding site mapped to the 3' UTR; C and D: mRNA and protein levels of CDK6 in colon cancer cell lines (HT29 and SW480) transfected with miR-320 family mimics and a mimic control; E: The relative CDK6 expression level compared with that in non-neoplastic mucosa in 16 matched samples; F-J: Pearson's correlation analysis between the expression levels of the miR-320 family and CDK6 in 16 matched samples ( $^*P < 0.05$ ). UTR: Untranslated regions; 320am: miR-320a mimics; 320bm: miR-320b mimics; 320cm: miR-320c mimics; 320dm: miR-320d mimics; 320em: miR-320e mimics; mc: Mimic control; C: Carcinoma; A: Adenoma; N: Adjacent non-neoplastic mucosa.

the miR-320 family is targeted to CDK6 in CRC and has an influence on cell cycle. We report that the miR-320 family suppresses colorectal tumor progression by targeting CDK6.

In our study, the effects on tumor proliferation by overexpression of miR-320e were not observed, whereas overexpression of miR-320c and miR-320d resulted in a particularly strong reduction of tumor proliferation. CDK6 expression after introduction of miR-320e mimics in colon cancer cell lines indicated a similar tendency to be decreased at the mRNA and protein levels, but these were not as significant as the marked changes observed in other members of the miR-320 family. Targets of miRNAs can be predicted by requiring conserved Watson-Crick pairing to the 5' region of the miRNA, known as the miRNA seed<sup>[30]</sup>. The seeds of miR-320e for CDK6 were maximum 6 mer. As the seeds of other members of the miR-320 family were maximum 8 mer, this difference in the structure of the miR-320 family might lead to differences in the effects on CDK6 expression. We believe that this results give support the relationship between miR-320 family and CDK6. Further validations of these are required.

In conclusion, we have shown that the miR-320 family, which suppresses tumor proliferation by targeting CDK6, is downregulated in colorectal adenoma and early colorectal carcinoma tissue. The miR-320 family may play an important role in the growth of colorectal tumors and can be considered a biomarker for the early detection of colorectal tumors.

## COMMENTS

### Background

According to the adenoma-carcinoma sequence, colorectal adenoma (CRA) is considered to be a precursor lesion of colorectal cancer (CRC); the removal of

CRAs by polypectomy has been shown to reduce the incidence and mortality due to CRCs. Thus, detection of colorectal tumors in the early stages has become increasingly important in treatment and prognosis. The adenoma-carcinoma sequence is accompanied by several genetic and epigenetic alterations, such as mutations of cancer-associated genes and epigenetic modifications, including changes in microRNAs (miRNAs). However, the involvement of miRNAs in the mechanism of this sequence remains undetermined.

### Research frontiers

miRNAs are frequently dysregulated in human cancers, and alterations of miRNA expression in colorectal tumors have been well documented. For example, miRNA profiles of CRC compared with those of normal mucosa and adenoma. However, limited reports exist on the sequential changes in miRNA expression during histological progression from normal colonic mucosa through colorectal adenoma to early carcinoma in a lesion from a patient. miR-320a has been shown to effectively regulate proliferation, cell cycle, invasion, migration, and epithelial-mesenchymal transition of CRC. However, the carcinogenic mechanisms of miR-320b, c, d, and e are poorly understood, particularly in CRC, and needed further exploration.

### Innovations and breakthroughs

The authors investigated for the first time the sequential changes of miRNA expression profiles in colonic lesions from matched samples; histologically, non-neoplastic mucosa, adenoma, and submucosal invasive carcinoma were microdissected from a tissue sample. They have shown for the first time that the miR-320b, miR-320c, miR-320d are downregulated from colorectal adenoma and miR-320e is downregulated from colorectal submucosal carcinoma tissue and the miR-320 family suppresses tumor proliferation by targeting CDK6.

### Applications

This study suggests that the miR-320 family affects colorectal tumor proliferation by targeting CDK6, plays an important role in the growth of colorectal tumors. From these results, miR-320 family is considered as a biomarker for early detection of colorectal tumor.

### Terminology

The adenoma-carcinoma sequence is accompanied by several genetic and epigenetic alterations, such as mutations of cancer-associated genes and epigenetic modifications, including changes in DNA methylation, histone modifications, and miRNAs. miRNAs are small (19-23 nucleotide) endogenous non-coding RNAs that regulate gene expression by targeting the 3' untranslated

region of mRNA. miRNAs play fundamental roles in various biological processes.

## Peer-review

The manuscript by Tadano *et al* investigated the expression of miRNA in colorectal adenoma and submucosal invasive carcinoma and revealed miR-320 family affects colorectal tumor proliferation by targeting CDK6. This article is overall interesting and gives new insight in the field of dysregulation of miRNAs and colorectal cancer.

## REFERENCES

- 1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
- 2 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735 DOI: 10.1016/0092-8674(90)90186-I]
- 3 **Zauber AG**, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegoijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]
- 4 **Tanaka S**, Oka S, Kaneko I, Hirata M, Mouri R, Kanao H, Yoshida S, Chayama K. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc* 2007; **66**: 100-107 [PMID: 17591481 DOI: 10.1016/j.gie.2007.02.032]
- 5 **Leslie A**, Carey FA, Pratt NR, Steele RJ. The colorectal adenoma-carcinoma sequence. *Br J Surg* 2002; **89**: 845-860 [PMID: 12081733 DOI: 10.1046/j.1365-2168.2002.02120.x]
- 6 **Gattolliat CH**, Uguen A, Pesson M, Trillet K, Simon B, Doucet L, Robaszekiewicz M, Corcos L. MicroRNA and targeted mRNA expression profiling analysis in human colorectal adenomas and adenocarcinomas. *Eur J Cancer* 2015; **51**: 409-420 [PMID: 25586944 DOI: 10.1016/j.ejca.2014.12.007]
- 7 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]
- 8 **Lu J**, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. *Nature* 2005; **435**: 834-838 [PMID: 15944708 DOI: 10.1038/nature03702]
- 9 **Earle JS**, Luthra R, Romans A, Abraham R, Ensor J, Yao H, Hamilton SR. Association of microRNA expression with microsatellite instability status in colorectal adenocarcinoma. *J Mol Diagn* 2010; **12**: 433-440 [PMID: 20413677 DOI: 10.2353/jmoldx.2010.090154]
- 10 **Diosdado B**, van de Wiel MA, Terhaar Sive Droste JS, Mongera S, Postma C, Meijerink WJ, Carvalho B, Meijer GA. MiR-17-92 cluster is associated with 13q gain and c-myc expression during colorectal adenoma to adenocarcinoma progression. *Br J Cancer* 2009; **101**: 707-714 [PMID: 19672269 DOI: 10.1038/sj.bjc.6605037]
- 11 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541]
- 12 **Kudo Se**, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Triadafilopoulos G, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Vieth M, Jass JR, Hurlstone PD. Nonpolypoid neoplastic lesions of the colorectal mucosa. *Gastrointest Endosc* 2008; **68**: S3-47 [PMID: 18805238 DOI: 10.1016/j.gie.2008.07.052]
- 13 **Takahashi T**, Noshio K, Yamamoto H, Mikami M, Taniguchi H, Miyamoto N, Adachi Y, Itoh F, Imai K, Shinomura Y. Flat-type colorectal advanced adenomas (laterally spreading tumors) have different genetic and epigenetic alterations from protruded-type advanced adenomas. *Mod Pathol* 2007; **20**: 139-147 [PMID: 17143260 DOI: 10.1038/modpathol.3800722]
- 14 **Nakagawa Y**, Akao Y, Taniguchi K, Kamatani A, Tahara T, Kamano T, Nakano N, Komura N, Ikuno H, Ohmori T, Jodai Y, Miyata M, Nagasaka M, Shibata T, Ohmiya N, Hirata I. Relationship between expression of onco-related miRNAs and the endoscopic appearance of colorectal tumors. *Int J Mol Sci* 2015; **16**: 1526-1543 [PMID: 25584614 DOI: 10.3390/ijms16011526]
- 15 **Zhang GJ**, Zhou H, Xiao HX, Li Y, Zhou T. MiR-378 is an independent prognostic factor and inhibits cell growth and invasion in colorectal cancer. *BMC Cancer* 2014; **14**: 109 [PMID: 24555885 DOI: 10.1186/1471-2407-14-109]
- 16 **Dai X**, Chiang Y, Wang Z, Song Y, Lu C, Gao P, Xu H. Expression levels of microRNA-375 in colorectal carcinoma. *Mol Med Rep* 2012; **5**: 1299-1304 [PMID: 22377847 DOI: 10.3892/mmr.2012.815]
- 17 **Zhang Y**, He X, Liu Y, Ye Y, Zhang H, He P, Zhang Q, Dong L, Liu Y, Dong J. microRNA-320a inhibits tumor invasion by targeting neuropilin 1 and is associated with liver metastasis in colorectal cancer. *Oncol Rep* 2012; **27**: 685-694 [PMID: 22134529 DOI: 10.3892/or.2011.1561]
- 18 **Sun JY**, Huang Y, Li JP, Zhang X, Wang L, Meng YL, Yan B, Bian YQ, Zhao J, Wang WZ, Yang AG, Zhang R. MicroRNA-320a suppresses human colon cancer cell proliferation by directly targeting  $\beta$ -catenin. *Biochem Biophys Res Commun* 2012; **420**: 787-792 [PMID: 22459450 DOI: 10.1016/j.bbrc.2012.03.075]
- 19 **Meng LH**, Zhang H, Hayward L, Takemura H, Shao RG, Pommier Y. Tetrandrine induces early G1 arrest in human colon carcinoma cells by down-regulating the activity and inducing the degradation of G1-S-specific cyclin-dependent kinases and by inducing p53 and p21Cip1. *Cancer Res* 2004; **64**: 9086-9092 [PMID: 15604277 DOI: 10.1158/0008-5472.can-04-0313]
- 20 **Tsikitis VL**, White I, Mori M, Potter A, Bhattacharyya A, Hamilton SR, Buckmeier J, Lance P, Thompson P. Differential expression of microRNA-320a, -145, and -192 along the continuum of normal mucosa to high-grade dysplastic adenomas of the colorectum. *Am J Surg* 2014; **207**: 717-722; discussion 722 [PMID: 24791633 DOI: 10.1016/j.amjsurg.2013.12.023]
- 21 **Zhao H**, Dong T, Zhou H, Wang L, Huang A, Feng B, Quan Y, Jin R, Zhang W, Sun J, Zhang D, Zheng M. miR-320a suppresses colorectal cancer progression by targeting Rac1. *Carcinogenesis* 2014; **35**: 886-895 [PMID: 24265291 DOI: 10.1093/carcin/bgt378]
- 22 **Hur K**, Toiyama Y, Schetter AJ, Okugawa Y, Harris CC, Boland CR, Goel A. Identification of a metastasis-specific MicroRNA signature in human colorectal cancer. *J Natl Cancer Inst* 2015; **107**: dju492 [PMID: 25663689 DOI: 10.1093/jnci/dju492]
- 23 **Wan LY**, Deng J, Xiang XJ, Zhang L, Yu F, Chen J, Sun Z, Feng M, Xiong JP. miR-320 enhances the sensitivity of human colon cancer cells to chemoradiotherapy in vitro by targeting FOXM1. *Biochem Biophys Res Commun* 2015; **457**: 125-132 [PMID: 25446103 DOI: 10.1016/j.bbrc.2014.11.039]
- 24 **Uraoka T**, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592-1597 [PMID: 16682427 DOI: 10.1136/gut.2005.087452]
- 25 **Nagel R**, le Sage C, Diosdado B, van der Waal M, Oude Vrielink JA, Bolijn A, Meijer GA, Agami R. Regulation of the adenomatous polyposis coli gene by the miR-135 family in colorectal cancer. *Cancer Res* 2008; **68**: 5795-5802 [PMID: 18632633 DOI: 10.1158/0008-5472.can-08-0951]
- 26 **Lim LP**, Lau NC, Garrett-Engle P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* 2005; **433**: 769-773 [PMID: 15685193 DOI: 10.1038/nature03315]
- 27 **Sherr CJ**. Cancer cell cycles. *Science* 1996; **274**: 1672-1677 [PMID: 8939849 DOI: 10.1126/science.274.5293.1672]
- 28 **Wu J**, Qian J, Li C, Kwok L, Cheng F, Liu P, Perdomo C, Kotton D, Vaziri C, Anderlind C, Spira A, Cardoso WV, Lü J. miR-129 regulates cell proliferation by downregulating Cdk6 expression.



*Cell Cycle* 2010; **9**: 1809-1818 [PMID: 20404570 DOI: 10.4161/cc.9.9.11535]

- 29 **Wang X**, Wu J, Lin Y, Zhu Y, Xu X, Xu X, Liang Z, Li S, Hu Z, Zheng X, Xie L. MicroRNA-320c inhibits tumorous behaviors of bladder cancer by targeting Cyclin-dependent kinase 6. *J Exp*

*Clin Cancer Res* 2014; **33**: 69 [PMID: 25178497 DOI: 10.1186/s13046-014-0069-6]

- 30 **Lewis BP**, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. *Cell* 2003; **115**: 787-798 [PMID: 14697198 DOI: 10.1016/S0092-8674(03)01018-3]

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Retrospective Cohort Study

# Opioid-sparing effect of selective cyclooxygenase-2 inhibitors on surgical outcomes after open colorectal surgery within an enhanced recovery after surgery protocol

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**Informed consent statement:** As the study is a retrospective review, a waiver of informed consent was approved by the Siriraj Institutional Review Board.

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**Data sharing statement:** The original anonymous dataset is available on request from the corresponding author at bolloon@hotmail.com.

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## Abstract

**AIM:** To evaluate the opioid-sparing effect of selective cyclooxygenase-2 (COX-2) inhibitors on short-term surgical outcomes after open colorectal surgery.

**METHODS:** Patients undergoing open colorectal resection within an enhanced recovery after surgery protocol from 2011 to 2015 were reviewed. Patients with combined general anesthesia and epidural anesthesia, and those with acute colonic obstruction or perforation were excluded. Patients receiving selective COX-2 inhibitor were compared with well-matched individuals without such a drug. Outcome measures included numeric pain score and morphine milligram equivalent (MME) consumption on postoperative day (POD) 1-3, gastrointestinal recovery (time to tolerate solid diet and time to defecate), complications and length of postoperative stay.

**RESULTS:** There were 75 patients in each group. Pain score on POD 1-3 was not significantly different between two groups. However, MME consumption and MME consumption per kilogram body weight on POD 1-3 was significantly less in patients receiving a selective COX-2 inhibitor ( $P < 0.001$ ). Median MME consumption per kilogram body weight on POD 1-3 was 0.09, 0.06 and nil, respectively in patients receiving a selective COX-2 inhibitor and 0.22, 0.25 and 0.07, respectively in the comparative group ( $P < 0.001$ ), representing at least 59% opioid

reduction. Patients prescribing a selective COX-2 inhibitor had a shorter median time to resumption of solid diet [1 (IQR 1-2) d vs 2 (IQR 2-3) d;  $P < 0.001$ ] and time to first defecation [2 (IQR 2-3) d vs 3 (IQR 3-4) d;  $P < 0.001$ ]. There was no significant difference in overall postoperative complications between two groups. However, median postoperative stay was significantly 1-d shorter in patients prescribing a selective COX-2 inhibitor [4 (IQR 3-5) d vs 5 (IQR 4-6) d;  $P < 0.001$ ].

**CONCLUSION:** Perioperative administration of oral selective COX-2 inhibitors significantly decreased intravenous opioid consumption, shortened time to gastrointestinal recovery and reduced hospital stay after open colorectal surgery.

**Key words:** Selective cyclooxygenase-2 inhibitor; Outcome; Colon surgery; Rectal surgery; Enhanced recovery after surgery; Opioid; Ileus; Non-steroidal anti-inflammatory drug; Pain

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**Core tip:** This comparative study validates the effectiveness of perioperative administration of oral selective cyclooxygenase-2 (COX-2) inhibitors as a part of multimodal analgesia in an enhanced recovery after surgery protocol to significantly reduce opioid requirement (but not pain score) after open colorectal surgery. Our findings also indicate that opioid-sparing effect of selective COX-2 inhibitor has some important clinical benefits including quicker gastrointestinal recovery and shorter hospitalization.

Lohsiriwat V. Opioid-sparing effect of selective cyclooxygenase-2 inhibitors on surgical outcomes after open colorectal surgery within an enhanced recovery after surgery protocol. *World J Gastrointest Oncol* 2016; 8(7): 543-549 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v8/i7/543.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v8.i7.543>

## INTRODUCTION

Effective pain control for open colorectal surgery plays a crucial role in improving patient's recovery. Various analgesic modalities have been utilized to reduce postoperative pain including epidural analgesia and administration of selective cyclooxygenase-2 (COX-2) inhibitors. However, a recent nationwide analysis of the outcomes of epidural analgesia in open colorectal surgery in the United States has shown that epidural analgesia does not add major clinical benefits over conventional analgesia, but it is associated with longer hospital stay and a higher incidence of ileus<sup>[1]</sup>. In a large international registry of the enhanced recovery after surgery (ERAS) Compliance Group, prolonged hospitalization was also observed in patients with epidural analgesia<sup>[2]</sup>. Moreover,

epidural analgesia needs to be performed by a qualified anesthesiologist and it could lead to some serious complications such as epidural hematoma and epidural abscess<sup>[3]</sup>. As a result, the application of epidural analgesia in clinical practice has been limited<sup>[1,4,5]</sup>.

On the other hand, a selective COX-2 inhibitor, a nonsteroidal anti-inflammatory drug (NSAID) directly targeting COX-2 which is an enzyme primarily responsible for inflammation and pain, are widely available in both oral preparation and injectable form<sup>[6]</sup>. Having little or no effect on platelet aggregation, a selective COX-2 inhibitor has currently been used as a part of multimodal analgesia for several surgical procedures including colorectal surgery - which prefers a non-opioid analgesic regimen<sup>[7-9]</sup>. Perioperative administration of selective COX-2 inhibitors can reduce opioid requirement<sup>[10]</sup>, facilitate gastrointestinal recovery and shorten hospital stay after colorectal surgery<sup>[11]</sup>. However, there are a limited number of studies examining these outcome benefits in the setting of an ERAS protocol<sup>[10]</sup>.

In Thailand, an ERAS protocol for colorectal surgery has been introduced into a daily practice since 2011<sup>[9,12]</sup>. Regarding perioperative analgesia in our ERAS protocol, selective COX-2 inhibitors will be provided based on patient's comorbidities and their healthcare coverage scheme. Meanwhile, thoracic epidural analgesia is seldom applied due to its technical demand and a limited number of physician anesthesiologists<sup>[4]</sup>. Like many developing and underdeveloped countries, a majority of colorectal procedures in Thailand remains an open surgery because of limited resources and the expense of laparoscopic surgery<sup>[13]</sup>. The objective of this study was therefore to examine the clinical outcomes of perioperative administration of an oral selective COX-2 inhibitor for open colorectal surgery within an ERAS protocol (without the need of epidural analgesia).

## MATERIALS AND METHODS

This non-randomized, comparative, prospective study included adult patients undergoing elective laparotomy for colorectal resection from January 2011 to September 2015 at the Faculty of Medicine Siriraj Hospital. The study was approved by the Siriraj Institutional Review Board (SIRB COA No. Si014/2013). Patients with combined general anesthesia and epidural anesthesia, and those with acute colonic obstruction or perforation were excluded. Clinical outcomes of patients receiving a selective COX-2 inhibitor were compared with those without such a drug, with a ratio of 1 to 1. They were matched for age, gender, body mass index (BMI), the ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (CR-POSSUM)<sup>[14]</sup>, and type of surgical procedure. Of note, all operations were performed by the author under an ERAS protocol. The ERAS protocol has been previously described<sup>[9,12,15]</sup>. In brief, only patients with left-sided colon or rectal resection received preoperative mechanical bowel preparation. Right-sided colon resection was preferentially

**Table 1 Perioperative pain control regimen**

Preoperative period	1 tablet of acetaminophen 500 mg ± 1 tablet of a selective cyclooxygenase-2 inhibitor (either celecoxib 400 mg, etoricoxib 90 mg or etoricoxib 120 mg)
Intraoperative period	Balanced general anesthesia Application of atraumatic O-ring wound retractor (if available)
Postoperative period	Infiltration of 0.5% bupivacaine into fascial layer and muscle around the wound edge 1 tablet of acetaminophen 500 mg every 6 h in the first 3 d ± 1 tablet of a selective cyclooxygenase-2 inhibitor daily for 5-7 d Intravenous patient-controlled morphine (or tramadol) or intermittent intravenous morphine if pain score > 3

done through a transverse incision. Otherwise, a midline laparotomy was performed. No intraabdominal drain or nasogastric tube was used. A diverting stoma was selectively fashioned in cases of coloanal anastomosis and neoadjuvant chemoradiation. Medication for prophylaxis of postoperative nausea and vomiting was administered based on patient's risk factor<sup>[16]</sup>. Standard postoperative care was provided including early feeding and scheduled ambulation.

### Perioperative analgesia

Approximately 3 h prior to surgery, one tablet of acetaminophen 500 mg with or without one tablet of an oral selective COX-2 inhibitor (either celecoxib 400 mg, etoricoxib 90 mg or etoricoxib 120 mg) were given. Of note, the administration of a selective COX-2 inhibitor was based on patient's co-morbidities, contraindication (*i.e.*, coronary artery disease, ischemic stroke, peripheral arterial disease, uncontrolled hypertension) and their healthcare coverage scheme. An operation was performed under a balanced general anesthesia. An atraumatic O-ring wound retractor was applied during the operation if available<sup>[17]</sup>. After a closure of abdominal wall muscle, 0.5% bupivacaine (3-4 mg/kg) was infiltrated into fascial layer and muscle around the wound edge. The wound was then closed primarily. Standard protocol for postoperative pain control was followed in all cases. Basically, intravenous morphine (0.03-0.05 mg/kg per dose every 1-2 h) was administered if pain score was > 3 (using a numeric rating scale of 0-10 with 0 = no pain 10 = worst possible pain). Intravenous patient-controlled morphine or intravenous tramadol (an equivalent of 10 mg tramadol to 1 mg morphine) may be used in some cases<sup>[18]</sup>. During the postoperative period, one tablet of acetaminophen 500 mg was given every 6 h in the first 3 d, with or without daily oral selective COX-2 inhibitor for 5-7 d. Perioperative analgesia protocol was summarized in Table 1.

### Outcome measures

Primary outcome measures included average pain score on postoperative day (POD) 1-3, intravenous opioid requirement on POD 1-3, gastrointestinal recovery (time to tolerate solid diet and time to defecate), complication according to the Clavien-Dindo classification system<sup>[19]</sup>, prolonged postoperative ileus<sup>[20]</sup>, and length of postoperative stay. Pain scores were recorded every 4 h by nursing staff. All pain assessments were noted after

patients were asked to take a deep breath. Should the patients slept at night during the scheduled time for pain assessment, they were not awakened and the actual time the patients were assessed was noted. Unless intravenous patient-controlled opioid was applied, intermittent intravenous morphine was given if pain score was > 3 as in the aforementioned regimen. Total daily intravenous opioid requirement was reported as morphine milligram equivalent (MME).

All patients were offered a clear liquid diet immediately after surgery providing that they were clinically stable. Once the oral intake exceeded 20 mL/kg body weight without nausea and vomiting, the diet was advanced to a low-residual solid diet. Prolonged postoperative ileus was defined as at least two times of nausea/vomiting, inability to tolerate oral diet and absence of flatus over 24 h, and abdominal distension with radiologic confirmation occurring on or after POD 4<sup>[20]</sup>. Patients were discharged from the hospital when they had no fever, adequate pain control with oral analgesics, good ambulation, and satisfactory recovery of gastrointestinal function. All patients were scheduled for follow-up at 30 d postoperatively.

### Statistical analysis

All data were prepared and compiled using Statistical Package for the Social Sciences (SPSS®) program version 18.0 for Windows (SPSS Inc., Chicago, IL). Values are expressed as median (interquartile range: IQR), mean (SD) or number (%). Continuous variables were compared using the *t*-test or Mann-Whitney *U* test. Categorical variables were compared using the  $\chi^2$  test. A *P*-value of less 0.05 was considered statistically significant.

## RESULTS

This study included 150 patients (57% male) with the average age of 65 years (range 30-87). There were 75 patients in each group. There was no significant difference in patient's characteristics, intraoperative detail, type of operation and percentage of adherence to the ERAS protocol between the two groups, except patients receiving a selective COX-2 inhibitor had a higher level of preoperative hematocrit and serum albumin (Table 2).

Pain score on POD 1-3 was not significantly different between the two groups. However, MME requirement on POD 1-3 was significantly less in patients receiving

**Table 2 Patient characteristics and operative details**

	Patients with selective COX-2 inhibitor ( <i>n</i> = 75)	Patients without selective COX-2 inhibitor ( <i>n</i> = 75)	<i>P</i> -value
Age (yr)	64 (55-73)	65 (59-75)	0.15
Male	43 (57)	42 (56)	0.87
Weight (kg)	68 (51-58)	59 (50-66)	0.93
Body mass index	23.1 (20.9-25.4)	22.5 (20.6-24.6)	0.49
CR-POSSUM predicted mortality	1.8 (1.0-2.5)	1.9 (1.3-3.4)	0.07
Hematocrit (%)	38 (34-41)	35 (31-39)	0.014 <sup>1</sup>
Serum albumin (g/L)	4.0 (3.6-4.3)	3.8 (3.4-4.1)	0.013 <sup>1</sup>
Operative time (min)	180 (120-220)	160 (120-180)	0.21
Blood loss (mL)	150 (50-250)	150 (50-260)	0.75
Operation for malignancy	67 (89)	68 (91)	0.37
Rectal resection	41 (55)	37 (49)	0.51
Operation without bowel restoration	11 (15)	12 (16)	0.82
Use of atraumatic O-ring retractor	66 (88)	59 (79)	0.13
Adherence to ERAS protocol (%)	88 (82-88)	82 (82-88)	0.28

<sup>1</sup>*P* < 0.05. COX-2: Cyclooxygenase-2; CR-POSSUM: The ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity; ERAS: Enhanced recovery after surgery.

**Table 3 Postoperative pain score and intravenous opioid requirement**

	Patients with selective COX-2 inhibitor ( <i>n</i> = 75)	Patients without selective COX-2 inhibitor ( <i>n</i> = 75)	<i>P</i> -value
Pain POD1	1.5 (0.7-2.1)	1.5 (0.5-2.7)	0.78
Pain POD2	0.7 (0-2.0)	0.6 (0-1.5)	0.74
Pain POD3	0.5 (0-1.5)	0.5 (0-1.7)	0.38
MME POD1	6 (2-12)	13 (6-20)	< 0.001 <sup>1</sup>
MME POD2	3 (0-17)	20 (4-20)	< 0.001 <sup>1</sup>
MME POD3	0 (0-0)	5 (0-15)	< 0.001 <sup>1</sup>
MME/KG POD1	0.09 (0.03-0.23)	0.22 (0.11-0.42)	< 0.001 <sup>1</sup>
MME/KG POD2	0.06 (0-0.28)	0.25 (0.07-0.37)	< 0.001 <sup>1</sup>
MME/KG POD3	0 (0-0)	0.07 (0-0.25)	< 0.001 <sup>1</sup>

<sup>1</sup>*P* < 0.05. COX-2: Cyclooxygenase-2; MME: Morphine milligram equivalent; MME/KG: Morphine milligram equivalent per kilogram body weight; POD: Postoperative day.

a selective COX-2 inhibitor (Table 3). Median MME consumption per kilogram body weight on POD 1-3 was 0.09, 0.06 and nil, respectively in patients receiving a selective COX-2 inhibitor and 0.22, 0.25 and 0.07, respectively in the comparative group (*P* < 0.001), representing at least 59% opioid reduction.

Patients receiving a selective COX-2 inhibitor had a shorter median time to resumption of solid diet [1 (IQR 1-2) d vs 2 (IQR 2-3) d; *P* < 0.001] and time to first defecation [2 (IQR 2-3) d vs 3 (IQR 3-4) d; *P* < 0.001]. There was no significant difference in the rate of overall postoperative complication and prolonged postoperative ileus between the two groups (Table 4). Of note, there were 1 non-fatal acute myocardial infarction and 1 colorectal anastomotic leakage requiring an operation in patients without selective COX-2 inhibitor. Median and average postoperative stay was significantly 1-d shorter in patients prescribing a selective COX-2 inhibitor; [4 (IQR 3-5) d vs 5 (IQR 4-6) d; *P* < 0.001] and [4.3 (SD 3.0) d vs 5.3 (SD 2.5) d; *P* = 0.023], respectively. Three patients (4%) in the selective COX-2 inhibitor group and 1 patient (1%) in the comparative group required readmission within 30 d after the operation (*P* = 0.62). No 30-d death was observed in this study.

## DISCUSSION

The main findings of this comparative study are that perioperative administration of an oral selective COX-2 inhibitor - as a part of multimodal analgesic regimen - reduces intravenous opioid requirement, shortens time to gastrointestinal recovery and decreases the length of hospital stay after open colorectal surgery within an ERAS protocol. These results were consistent with a report from a prospective randomized, double-blind, placebo-controlled study examining the influence of pre- and post-administration of a selective COX-2 inhibitor (valdecoxib 40 mg) in major colorectal surgery within a non or partial ERAS protocol<sup>[11]</sup>. The randomized clinical trial indicated that patients treated with valdecoxib had a one-third opioid reduction, a 12-h quicker time to first bowel movement and a 2-d shorter hospital stay. However, valdecoxib has been off the market since 2005 due to its potentially life-threatening skin reaction and lack of adequate data on its long-term cardiovascular safety<sup>[21]</sup>.

Many studies have shown that preemptive analgesia is more effective than postoperative analgesia<sup>[22-24]</sup>. A combination of preoperative and postoperative admini-



**Table 4** Gastrointestinal recovery, complication and hospital stay

	Patients with selective COX-2 inhibitor (n = 75)	Patients without selective COX-2 inhibitor (n = 75)	P-value
Time to tolerate solid diet (d)	1 (1-2)	2 (2-3)	< 0.001 <sup>1</sup>
Time to defecate (d)	2 (2-3)	3 (3-4)	< 0.001 <sup>1</sup>
Overall complication	9 (11)	17 (23)	0.08
Grade I	4	7	
Grade II	5	7	
Grade III	0	2	
Grade IV	0	1	
Prolonged postoperative ileus	4 (5)	6 (8)	0.75
Postoperative stay (d)			
Median (IQR)	4 (3-5)	5 (4-6)	< 0.001 <sup>1</sup>
Mean (SD)	4.3 (3.0)	5.3 (2.5)	0.023 <sup>1</sup>
Readmission within 30 d	3 (4)	1 (1)	0.62

<sup>1</sup>P < 0.05. If a patient had more than one complication, the highest Clavien-Dindo grade was reported. COX-2: Cyclooxygenase-2.

stration of analgesics would have a better pain control. A beneficial outcome effect of perioperative administration of currently available selective COX-2 inhibitors including celecoxib and etoricoxib may be attributed to adequate perioperative nociceptive afferent blockage and to minimize central sensitization (as a preoperative use), and to maintain anti-inflammatory effect after an operation (as a postoperative use). Unlike conventional NSAIDs, a selective COX-2 inhibitor has little or no effect on platelet aggregation and gastrointestinal irritation<sup>[25,26]</sup>. These characteristics of selective COX-2 inhibitors are therefore favorable to perioperative administration.

Although there was no difference in postoperative pain score between the two groups, this study showed that a regimen of perioperative pain control in both groups was very effective - which achieved a reasonable level of comfort in the postoperative period (with a median pain score of < 2). However, patients receiving a selective COX-2 inhibitor required less parenteral opioid. Since opioid is well known to cause postoperative nausea/vomiting and gastrointestinal dysfunction<sup>[27]</sup>, as a result, in part, shorter gastrointestinal convalescence was observed in patients prescribing a selective COX-2 inhibitor. While a reduction in opioid consumption may be responsible for shorter time to gastrointestinal recovery, a selective COX-2 inhibitor alone was shown to diminish a local inflammatory response of the small bowel to surgical manipulation, thus leading to quicker recovery of postoperative intestinal dysfunction<sup>[28]</sup>. In animal studies, selective COX-2 inhibitors induced duodenal motility and improved small bowel propulsion in rats subjected to abdominal surgery<sup>[29,30]</sup>.

In this study, there was a non-significant trend in decreased rates of overall complication and prolonged postoperative ileus in patients receiving a selective COX-2 inhibitor. The clinical relevance of NSAID-induced opioid sparing on favorable postoperative outcomes, including less incidence of postoperative gastrointestinal dysfunction and other complications, has been shown in several studies of non-colorectal surgery<sup>[31-35]</sup> and colorectal surgery<sup>[11]</sup>. Apart from its opioid-sparing effects,

selective COX-2 inhibitors may be associated with a reduction in postoperative complication by minimizing both inflammatory response and endocrine-metabolic response to surgery<sup>[36]</sup>.

While it seems clear that a selective COX-2 inhibitor has a positive impact on opioid consumption and gastrointestinal recovery in this study, patients prescribing a selective COX-2 inhibitor are generally at a higher risk for cardiovascular and thromboembolic events compared with a control or placebo drug<sup>[37]</sup>. Therefore, selective COX-2 inhibitors should not be used in individuals at increased risk for vascular thrombosis, *e.g.*, coronary artery disease, cerebrovascular disease and peripheral arterial disease. The physicians are also encouraged to use the lowest effective dose for the shortest duration of a selective COX-2 inhibitor. In surgical point of view, the use of any NSAIDs including selective COX-2 inhibitors in the setting of gastrointestinal anastomosis has been concerned because some studies have suggested that NSAIDs may impair anastomotic healing<sup>[38-40]</sup>. Recently, a meta-analysis of clinical and experimental studies in 2014 has indicated a strong link between anastomotic leakage and the use of non-selective NSAIDs, but not the use of selective COX-2 inhibitors<sup>[41]</sup>. So far, the ERAS society guidelines include NSAIDs and selective COX-2 inhibitors as a component of multimodal analgesia in elective colorectal surgery<sup>[7,8]</sup>.

Limitations of this study include the fact that it is a non-randomized study. Selective bias and performance bias could occur in the study. However, all patients were operated on by the same surgeon with a relatively high adherence to the ERAS protocol (> 80% compliance in both groups). Moreover, the patients were systematically assessed with a pre-defined objective measurement. It should be noted that not all patients received intravenous patient-controlled analgesia due to a limited number of equipment. To overcome this problem, a standardized protocol for postoperative pain control has been adopted in our institute since 2004. Another limitation is that only patients undergoing open colorectal surgery were included in this study. Whether patients undergoing minimally

invasive surgery, who will have a less inflammatory and metabolic response to surgery compared with open surgery<sup>[42]</sup>, will be beneficial to the administration of selective COX-2 inhibitors are not investigated.

In conclusion, this study validates the effectiveness of perioperative administration of currently available oral selective COX-2 inhibitors as a part of multimodal analgesia in an ERAS protocol to significantly reduce opioid requirement (but not pain score) after open colorectal surgery. Our findings also indicate that opioid-sparing effect of selective COX-2 inhibitor has some important clinical benefits including quicker gastrointestinal recovery and shorter hospitalization.

## COMMENTS

### Background

Effective perioperative pain control plays a crucial role in improving patient's recovery especially for an open abdominal surgery. Opioid is very effective analgesia but it has several undesired side effects such as sedation, itching, nausea, vomiting and constipation. Non-opioid analgesia has been recommended as a part of multimodal analgesia in an enhanced recovery after surgery (ERAS) protocol. Selective cyclooxygenase-2 (COX-2) inhibitors have some advantages over conventional non-steroidal anti-inflammatory drugs because they have little or no effect on platelet aggregation and gastrointestinal irritation.

### Research frontiers

Several studies have shown perioperative administration of selective COX-2 inhibitors can reduce opioid requirement, facilitate gastrointestinal recovery and shorten hospital stay after colorectal surgery. However, there are a limited number of studies examining these outcome benefits in the setting of an ERAS protocol.

### Innovations and breakthroughs

The present study validates the effectiveness of perioperative administration of currently available oral selective COX-2 inhibitors as a part of multimodal analgesia in an ERAS protocol to significantly reduce opioid requirement (but not pain score) after open colorectal surgery. This study also indicates that opioid-sparing effect of selective COX-2 inhibitor has some important clinical benefits including quicker gastrointestinal recovery and shorter hospitalization.

### Applications

The study results suggest that perioperative administration of selective COX-2 inhibitors is an effective perioperative pain control regimen - which could be used as a part of multimodal analgesia for open colorectal surgery if no contraindication.

### Peer-review

This is a good article.

## REFERENCES

- Halabi WJ, Jafari MD, Nguyen VQ, Carmichael JC, Mills S, Stamos MJ, Pigazzi A. A nationwide analysis of the use and outcomes of epidural analgesia in open colorectal surgery. *J Gastrointest Surg* 2013; **17**: 1130-1137 [PMID: 23595885 DOI: 10.1007/s11605-013-2195-4]
- ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. *Ann Surg* 2015; **261**: 1153-1159 [PMID: 25671587]
- Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. *Anaesthesia* 2007; **62**: 335-341 [PMID: 17381568 DOI: 10.1111/j.1365-2044.2007.04992.x]
- Charuluxananan S, Punjasawadwong Y, Suraseranivongse S, Srisawasdi S, Kyokong O, Chinachoti T, Chanchayanon T, Rungreungvanich M, Thienthong S, Sirinan C, Rodanant O. The Thai Anesthesia Incidents Study (THAI Study) of anesthetic outcomes: II. Anesthetic profiles and adverse events. *J Med Assoc Thai* 2005; **88** Suppl 7: S14-S29 [PMID: 16862682]
- Halabi WJ, Kang CY, Nguyen VQ, Carmichael JC, Mills S, Stamos MJ, Pigazzi A. Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. *JAMA Surg* 2014; **149**: 130-136 [PMID: 24336894 DOI: 10.1001/jamasurg.2013.3186]
- Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res* 2007; **5**: 19-34 [PMID: 17456832 DOI: 10.3121/cm.2007.698]
- Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, McNaught CE, Macfie J, Liberman AS, Soop M, Hill A, Kennedy RH, Lobo DN, Fearon K, Ljungqvist O. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 259-284 [PMID: 23052794 DOI: 10.1007/s00268-012-1772-0]
- Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, Ljungqvist O, Soop M, Ramirez J. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 285-305 [PMID: 23052796 DOI: 10.1007/s00268-012-1787-6]
- Lohsiriwat V. Enhanced recovery after surgery vs conventional care in emergency colorectal surgery. *World J Gastroenterol* 2014; **20**: 13950-13955 [PMID: 25320532 DOI: 10.3748/wjg.v20.i38.13950]
- Larson DW, Lovely JK, Cima RR, Dozois EJ, Chua H, Wolff BG, Pemberton JH, Devine RR, Huebner M. Outcomes after implementation of a multimodal standard care pathway for laparoscopic colorectal surgery. *Br J Surg* 2014; **101**: 1023-1030 [PMID: 24828373 DOI: 10.1002/bjs.9534]
- Sim R, Cheong DM, Wong KS, Lee BM, Liew QY. Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific inhibitor as opioid-sparing analgesia in major colorectal surgery. *Colorectal Dis* 2007; **9**: 52-60 [PMID: 17181846 DOI: 10.1111/j.1463-1318.2006.00998.x]
- Lohsiriwat V. The influence of preoperative nutritional status on the outcomes of an enhanced recovery after surgery (ERAS) programme for colorectal cancer surgery. *Tech Coloproctol* 2014; **18**: 1075-1080 [PMID: 25216721 DOI: 10.1007/s10151-014-1210-4]
- Lohsiriwat V, Lohsiriwat D, Thavichaigarn P. Current practices in rectal cancer surgery: a survey of Thai colorectal surgeons. *J Med Assoc Thai* 2009; **92**: 1009-1015 [PMID: 19694323]
- Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, Windsor AC. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). *Br J Surg* 2004; **91**: 1174-1182 [PMID: 15449270 DOI: 10.1002/bjs.4430]
- Lohsiriwat V. Impact of an enhanced recovery program on colorectal cancer surgery. *Asian Pac J Cancer Prev* 2014; **15**: 3825-3828 [PMID: 24870801 DOI: 10.7314/APJCP.2014.15.8.3825]
- Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014; **118**: 85-113 [PMID: 24356162 DOI: 10.1213/ANE.0000000000000002]
- Lohsiriwat V, Lohsiriwat D. Atraumatic O-ring wound retractor reduces postoperative pain. *Tech Coloproctol* 2014; **18**: 1177-1178 [PMID: 25326110 DOI: 10.1007/s10151-014-1225-x]
- Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; **43**: 879-923 [PMID: 15509185 DOI: 10.2165/00003088-200443130-00004]
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15072932 DOI: 10.1097/SLA.0000000000000002]

- 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
- 20 **Vather R**, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. *J Gastrointest Surg* 2013; **17**: 962-972 [PMID: 23377782 DOI: 10.1007/s11605-013-2148-y]
- 21 **Chakraborti AK**, Garg SK, Kumar R, Motiwala HF, Jadhavar PS. Progress in COX-2 inhibitors: a journey so far. *Curr Med Chem* 2010; **17**: 1563-1593 [PMID: 20166930 DOI: 10.2174/092986710790979980]
- 22 **Lohsiriwat V**, Lert-akyamanee N, Rushatamukayanunt W. Efficacy of pre-incisional bupivacaine infiltration on postoperative pain relief after appendectomy: prospective double-blind randomized trial. *World J Surg* 2004; **28**: 947-950 [PMID: 15573244 DOI: 10.1007/s00268-004-7471-8]
- 23 **Karaman Y**, Kebapci E, Gurkan A. The preemptive analgesic effect of lornoxicam in patients undergoing major abdominal surgery: a randomised controlled study. *Int J Surg* 2008; **6**: 193-196 [PMID: 18434268 DOI: 10.1016/j.ijsu.2008.03.001]
- 24 **Akaraviputh T**, Leelouhapong C, Lohsiriwat V, Aroonpruksakul S. Efficacy of perioperative parecoxib injection on postoperative pain relief after laparoscopic cholecystectomy: a prospective, randomized study. *World J Gastroenterol* 2009; **15**: 2005-2008 [PMID: 19399934 DOI: 10.3748/wjg.15.2005]
- 25 **Wickerts L**, Warrén Stomberg M, Brattwall M, Jakobsson J. Coxibs: is there a benefit when compared to traditional non-selective NSAIDs in postoperative pain management? *Minerva Anesthesiol* 2011; **77**: 1084-1098 [PMID: 21617597]
- 26 **Chan FK**, Lanis A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* 2010; **376**: 173-179 [PMID: 20638563 DOI: 10.1016/S0140-6736(10)60673-3]
- 27 **Dorn S**, Lembo A, Cremonini F. Opioid-Induced Bowel Dysfunction: Epidemiology, Pathophysiology, Diagnosis, and Initial Therapeutic Approach. *Am J Gastroenterol* 2014; **2**: 31-37 [PMID: 25207610 DOI: 10.1038/ajg.2014.7]
- 28 **Schmidt J**, Stoffels B, Nazir A, Dehaven-Hudkins DL, Bauer AJ. Alvimopan and COX-2 inhibition reverse opioid and inflammatory components of postoperative ileus. *Neurogastroenterol Motil* 2008; **20**: 689-699 [PMID: 18266613 DOI: 10.1111/j.1365-2982.2007.01078.x]
- 29 **Nylander O**. The impact of cyclooxygenase inhibition on duodenal motility and mucosal alkaline secretion in anaesthetized rats. *Acta Physiol (Oxf)* 2011; **201**: 179-192 [PMID: 20887356 DOI: 10.1111/j.1748-1716.2010.02196.x]
- 30 **Korolkiewicz RP**, Ujda M, Dabkowski J, Ruczyński J, Rekowski P, Petrusiewicz J. Differential salutary effects of nonselective and selective COX-2 inhibitors in postoperative ileus in rats. *J Surg Res* 2003; **109**: 161-169 [PMID: 12643859 DOI: 10.1016/S0022-4804(02)00095-1]
- 31 **Gilron I**, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC. A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. *Pain* 2005; **113**: 191-200 [PMID: 15621380 DOI: 10.1016/j.pain.2004.10.008]
- 32 **Chen JY**, Wu GJ, Mok MS, Chou YH, Sun WZ, Chen PL, Chan WS, Yien HW, Wen YR. Effect of adding ketorolac to intravenous morphine patient-controlled analgesia on bowel function in colorectal surgery patients--a prospective, randomized, double-blind study. *Acta Anaesthesiol Scand* 2005; **49**: 546-551 [PMID: 15777304 DOI: 10.1111/j.1399-6576.2005.00674.x]
- 33 **Cepeda MS**, Carr DB, Miranda N, Diaz A, Silva C, Morales O. Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial. *Anesthesiology* 2005; **103**: 1225-1232 [PMID: 16306736 DOI: 10.1097/00000542-200512000-00018]
- 34 **Huang YM**, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. *BMC Musculoskelet Disord* 2008; **9**: 77 [PMID: 18519002 DOI: 10.1186/1471-2474-9-77]
- 35 **Chau-in W**, Thienthong S, Pulnitiporn A, Tantanatewin W, Prasertcharoensuk W, Sriraj W. Prevention of post operative pain after abdominal hysterectomy by single dose etoricoxib. *J Med Assoc Thai* 2008; **91**: 68-73 [PMID: 18386547]
- 36 **Kehlet H**, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; **87**: 62-72 [PMID: 11460814 DOI: 10.1093/bja/87.1.62]
- 37 **Trelle S**, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Jüni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011; **342**: c7086 [PMID: 21224324 DOI: 10.1136/bmj.c7086]
- 38 **Hakkarainen TW**, Steele SR, Bastaworous A, Dellinger EP, Farrokhi E, Farjah F, Florence M, Helton S, Horton M, Pietro M, Varghese TK, Flum DR. Nonsteroidal anti-inflammatory drugs and the risk for anastomotic failure: a report from Washington State's Surgical Care and Outcomes Assessment Program (SCOAP). *JAMA Surg* 2015; **150**: 223-228 [PMID: 25607250 DOI: 10.1001/jamasurg.2014.2239]
- 39 **Paulasir S**, Kaoutzanis C, Welch KB, Vandewarker JF, Krapohl G, Lampman RM, Franz MG, Cleary RK. Nonsteroidal Anti-inflammatory Drugs: Do They Increase the Risk of Anastomotic Leaks Following Colorectal Operations? *Dis Colon Rectum* 2015; **58**: 870-877 [PMID: 26252849 DOI: 10.1097/DCR.0000000000000430]
- 40 **Gorissen KJ**, Benning D, Berghmans T, Snoeijis MG, Sosef MN, Hulstew K, Luyer MD. Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. *Br J Surg* 2012; **99**: 721-727 [PMID: 22318712 DOI: 10.1002/bjs.8691]
- 41 **Bhangu A**, Singh P, Fitzgerald JE, Slessor A, Tekkis P. Postoperative nonsteroidal anti-inflammatory drugs and risk of anastomotic leak: meta-analysis of clinical and experimental studies. *World J Surg* 2014; **38**: 2247-2257 [PMID: 24682313 DOI: 10.1007/s00268-014-2531-1]
- 42 **Braga M**, Vignali A, Zuliani W, Radaelli G, Gianotti L, Martani C, Toussoun G, Di Carlo V. Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. *Dis Colon Rectum* 2002; **45**: 1070-1077 [PMID: 12195192 DOI: 10.1007/s10350-004-6362-2]

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## Retrospective Study

# Management of colorectal neoplasia during pregnancy and in the postpartum period

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## Abstract

**AIM:** To report our experience on management of colorectal neoplasia during pregnancy and in the postpartum period.

**METHODS:** Patients who were diagnosed with colorectal cancer during pregnancy or in the postpartum period (< 6 mo), between 8/1997 and 4/2013, in our department were reviewed. Patient characteristics, operations, fetal health and follow-up during pregnancy, type of delivery and oncologic outcomes were analyzed.

**RESULTS:** Eight patients met our study criteria. Median age at the time of diagnosis of colorectal cancer was 31 years. Median follow-up after surgery was 36 mo. Median duration of symptoms before diagnosis was 16 wk. Three patients were diagnosed with colorectal cancer during pregnancy and underwent surgery prior to delivery. None of the patients received adjuvant treatment during pregnancy. Five patients were diagnosed with colorectal cancer within a median of 2.1 mo after delivery and underwent surgery. No adverse neonatal outcomes were noted. All deliveries were at term (2 cesarean sections) except for one preterm delivery following low anterior resection on the 34<sup>th</sup> week of pregnancy.

**CONCLUSION:** There has been a significant delay in the diagnosis of colorectal cancer which is probably due to overlap of symptoms and signs between these tumors and a normal pregnancy. Surgery for colorectal cancer during pregnancy can be performed safely without compromising



maternal and fetal outcomes.

**Key words:** Colorectal cancer; Pregnancy; Postpartum; Neoplasia

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**Core tip:** This paper summarizes the experience of a tertiary referral colorectal center in the United States on the management of colorectal neoplasia during the pregnancy and postpartum period. Eight patients who were diagnosed with colorectal cancer during pregnancy or in the postpartum period between 8/1997 and 4/2013 were reviewed. No maternal and neonatal mortality occurred related to surgical treatment. While surgery for colorectal cancer during pregnancy can be performed safely and may not affect maternal and fetal outcomes adversely, there has been a significant delay in the diagnosis of colorectal cancer which is probably due to overlap of symptoms and signs between these tumors and a normal pregnancy.

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## INTRODUCTION

While the incidence of colorectal cancer is steady or falling, some studies report an increased incidence of colorectal cancer in younger patients (< 40 years)<sup>[1]</sup>, which may occur during the reproductive age and therefore interfere with pregnancy. Around 0.1% of pregnant women develop a malignancy and there is limited experience on the management of colorectal cancer diagnosed during pregnancy or in the postpartum period<sup>[2]</sup>. When colorectal cancer is detected in this period, treatment options may be limited. As two patients with possibly conflicting interests need to be managed, many ethical, psycho emotional and medical issues need to be simultaneously addressed. In this study, we analyzed management, complications, maternal and fetal outcomes in patients who were diagnosed with colorectal cancer during pregnancy or in the immediate postpartum period.

## MATERIALS AND METHODS

After obtaining the institutional review board approval (IRB), patients who were diagnosed with colorectal cancer during pregnancy or in the postpartum period and treated at the Department of Colorectal Surgery Cleveland Clinic Ohio, from August 1997 to April 2013, were analyzed in the study. The postpartum period is defined as first 6 mo after delivery<sup>[3]</sup>. Patient characteristics, cancer

follow-up, history of previous pregnancies, medications used during pregnancy, indication for surgery, operations performed, outcomes after surgery, complications, maternal and fetal morbidity and mortality during perinatal period and type of delivery were analyzed. Data were retrieved from the IRB approved prospectively maintained databases with supplemental information from patient charts. A multidisciplinary team including gastroenterologists, oncologists, obstetricians and colorectal surgeons followed up all patients.

Quantitative data were reported as median (range) and categorical data as numbers.

## RESULTS

Eight patients met our study criteria. Median age at the time of diagnosis of colorectal cancer was 31 (24-38) and median body mass index was 24 (19-27) kg/m<sup>2</sup>. Median follow-up after surgery was 36 mo (0.2-192). Two patients had a family history of hereditary non-polyposis colorectal cancer and one had juvenile polyposis syndrome. Four patients were nulliparous, the remaining 4 patients had a history of previous successful pregnancies. The presenting symptoms, duration of symptoms, tumor location and treatment strategy are listed in the Table 1. Median duration of symptoms before diagnosis was 16 (4-43) wk. Three patients were diagnosed with colorectal cancer during pregnancy and underwent surgery prior to delivery. These cases included 1 anterior resection with an end colostomy in the 18<sup>th</sup> week, 1 low anterior resection in the 24<sup>th</sup> week and 1 subtotal colectomy during the 8th week of pregnancy. Five patients were diagnosed with colorectal cancer within a median of 2.1 (1-4.2) mo after delivery. One synchronous low anterior resection and liver resection, 1 extensive left colectomy, 1 transanal resection, 1 ileocecal resection, and 1 right colectomy were performed on those patients. No adverse neonatal outcomes were noted. All deliveries were at term, except for one patient who underwent low anterior resection during pregnancy (34<sup>th</sup> week) and delivered preterm. Two patients underwent a cesarean section. Median APGAR score was 9 (8-9). Median birth weight was 3100 (3000-3800) g.

Adjuvant or neoadjuvant treatments were administered exclusively after delivery. In particular, one patient received neoadjuvant chemoradiotherapy whereas adjuvant chemotherapy was given to 5 patients. The specific chemotherapeutic regimens were 5-fluorouracil with leucovorin (*n* = 2), FOLFOX (*n* = 2) and FOLFIRI (*n* = 1). In long-term follow-up, two patients had further successful pregnancies. One of these patients had a ventral hernia repair. The patient initially treated with transanal excision of a T1 rectal lesion opted in favor of radical surgery after delivery and underwent low anterior resection.

## DISCUSSION

Our study shows that surgical intervention can be safe and feasible in patients who are diagnosed with



**Table 1** Treatment strategy and patient status at last follow-up

	Stage	Start of symptom (pregnancy week)	Duration of symptoms until diagnosis (wk)	Symptom	Tumor location	NCRT	Postoperative chemotherapy	Postoperative radiotherapy	Status at last follow-up
1 <sup>1,2</sup>	I	4	10	Rectal bleeding	Sigmoid colon	-	-	-	Alive (NED)
2 <sup>1,2</sup>	III	13	4	Rectal bleeding	Rectum	-	+	-	Alive (NED)
3 <sup>1,2</sup>	III	16	7	Rectal bleeding	Rectum	-	+	-	Alive (NED)
4 <sup>1,3</sup>	I	36	17	Rectal bleeding	Rectum	-	-	-	Alive (NED)
5 <sup>1,3</sup>	III	34	14	Abdominal pain	Right colon	-	-	-	Alive (NED)
6 <sup>1,3</sup>	III	20	24	Rectal bleeding	Rectum	-	+	-	Alive (NED)
7 <sup>1,3</sup>	IV	30	17	Rectal bleeding	Rectum	+	+	-	Deceased <sup>4</sup>
8 <sup>3</sup>	IV	12	43	Anemia, abdominal pain	Right colon	-	+	-	Deceased

<sup>1</sup>Curative surgery; <sup>2</sup>Diagnosed during pregnancy; <sup>3</sup>Diagnosed after pregnancy; <sup>4</sup>Recurrent disease. NCRT: Neoadjuvant chemoradio therapy; NED: No evidence of disease.

colorectal cancer during pregnancy or in the postpartum period. All of our patients who were diagnosed with colorectal cancer after delivery, had symptoms during pregnancy. Normal pregnancy can mask the symptoms and signs associated with colorectal malignancy<sup>[2,4,5]</sup>. For example, abdominal pain, intermittent rectal bleeding and anemia can occur during the course of pregnancy<sup>[6]</sup>. Occasional abdominal pain can be related to an enlarging uterus and uterine cramps. Hemorrhoids or anal fissure can be common causes of rectal bleeding in pregnant women<sup>[7]</sup>. Pregnancy can limit the utilization of standard diagnostic and therapeutic tools due to a gravid uterus and a potentially vulnerable fetus<sup>[8]</sup>, which in particular can hamper the liberal use of colonoscopy and computed tomography. However, all patients in our study group underwent complete colonoscopic evaluation before surgery. The age of diagnosis and tumor characteristics in our patients are similar to other series<sup>[5]</sup>.

Ultrasonography (USG), magnetic resonance imaging (MRI) or computed tomography (CT) were used for disease staging in our series. USG, MRI and CT can be used during pregnancy after consenting the patients about the associated risks and benefits. Heat effects of the magnetic field can be risky for the fetus, especially in the first trimester<sup>[9,10]</sup>. CT scan has a limited role in pregnancy due to radiation and contrast<sup>[11]</sup>. Proctosigmoidoscopy may be very helpful for differential diagnosis since more than 85% of colorectal tumors diagnosed during pregnancy appear to develop below the peritoneal reflection<sup>[12]</sup>. In addition, common anorectal problems can be excluded with a careful anorectal exam. In our series, 5 patients had rectal and 1 patient had a sigmoid colon cancer. Diagnosis of colorectal cancer at an early stage would result in better outcomes. Gastrointestinal symptoms should not be overlooked in a pregnant woman and should be evaluated with proper diagnostic modalities.

According the American Society of Gastrointestinal Endoscopy guidelines, an endoscopic intervention is safer than radiologically guided or surgical operations<sup>[13]</sup>. It is preferable to postpone endoscopy to the second trimester<sup>[12]</sup>. However, patients should be informed about the potential side effects including over sedation leading to hypoventilation or hypotension, teratogenic effects of medications used for sedation and premature birth<sup>[13]</sup>. We did not experience any complications patient or fetus related in our diagnostic work-up. Familial adenomatous polyposis is a known risk factor for colorectal cancer during pregnancy<sup>[14]</sup>. In our cohort, 2 patients had a family history of HNPCC and both of these patients were later confirmed with positive genetic testing. One of our patients had juvenile polyposis syndrome and diagnosed with a right colon cancer but later expired due to metastatic disease. In this particular patient diagnosis was delayed 43 mo and was diagnosed in the postpartum period.

The treatment strategy for colorectal cancer should be no different for pregnant and non-pregnant patients in terms of the aim which is potential curative treatment of the disease. However, the well-being of the fetus should be considered. Termination of ongoing pregnancy or delay of required treatment should be discussed with the patient according to time of pregnancy and patient's preference<sup>[2,6,15]</sup>. The first trimester of pregnancy is not appropriate for chemotherapy because of high risk of fetal malformations<sup>[16]</sup>. While it is generally recommended that chemotherapy should be given only after delivery, there are some reports suggesting that chemotherapy can be given in the second trimester without causing significant long-term complications<sup>[6,17,18]</sup>. However, it has been reported that the administration of 5-fluorouracil during pregnancy may cause spontaneous abortion<sup>[12]</sup>. If maternal and/or fetal healths are threatened, pre-

term delivery can be considered<sup>[6]</sup>. Walsh *et al.*<sup>[19]</sup> have proposed an algorithm to manage colorectal cancer diagnosed during pregnancy and recommend individualized treatment based on the disease stage and time of diagnosis during pregnancy. Acting as a team during follow-up and including the patient in decision making are advised.

While low patient number and retrospective design are the major drawbacks of the study, our study is one of the largest single center experiences on this topic. In our limited experience with three patients who have undergone surgery during pregnancy, no adverse maternal and fetal outcomes were observed. There has been a significant delay in the diagnosis of these tumors which is probably due to overlap of symptoms and signs between colorectal malignancy and a normal pregnancy.

## ACKNOWLEDGMENTS

Poster presentation at the meeting of the American Society of Colon and Rectal Surgeons, 2014. Erman Aytac is an assistant professor of surgery at the Acibadem University in Istanbul, Turkey.

## COMMENTS

### Background

Colorectal cancer in pregnancy is a rare condition and the literature on this subject is scant with fewer than 300 cases reported. The diagnosis of colorectal cancer in pregnancy is usually delayed because the individuals are young and the diagnosis is not entertained. As two patients with possibly conflicting interests need to be managed, many ethical, psycho emotional and medical issues need to be simultaneously addressed. In this study, they analyzed management, complications, maternal and fetal outcomes in patients who were diagnosed with colorectal cancer during pregnancy or in the immediate postpartum period.

### Research frontiers

Around 0.1% of pregnant women develop a malignancy and there is limited experience on the management of colorectal cancer diagnosed during pregnancy or perinatal period. When colorectal cancer is detected in this period, treatment options may be limited.

### Innovations and breakthroughs

In the authors' experience with three patients who have undergone surgery during pregnancy, no adverse maternal and fetal outcomes were observed. There has been a significant delay in the diagnosis of these tumors which is probably due to overlap of symptoms and signs between colorectal malignancy and a normal pregnancy.

### Applications

The treatment strategy for colorectal cancer should be no different for pregnant and non-pregnant patients in terms of the aim which is potential curative treatment of the disease. Considering the significant delay in the diagnosis of these tumors during pregnancy, new diagnostic modalities with reduced fetal side effects would facilitate diagnosis of colorectal cancer.

### Terminology

Patients who were diagnosed with colorectal cancer during pregnancy or in the postpartum period were analyzed in the study. The postpartum period is defined as first 6 mo after delivery.

## Peer-review

In this retrospective study by Aytac *et al* the authors are presenting their experiences in the management of colorectal neoplasia during pregnancy and in the postpartum period. This is a well written paper with insightful, thoughtful and helpful observations which are a result of serious and hard work from an experienced team of experts in the field of colorectal surgery.

## REFERENCES

- 1 **Tawadros PS**, Paquette IM, Hanly AM, Mellgren AF, Rothenberger DA, Madoff RD. Adenocarcinoma of the rectum in patients under age 40 is increasing: impact of signet-ring cell histology. *Dis Colon Rectum* 2015; **58**: 474-478 [PMID: 25850833 DOI: 10.1097/DCR.0000000000000318]
- 2 **Salani R**, Billingsley CC, Crafton SM. Cancer and pregnancy: an overview for obstetricians and gynecologists. *Am J Obstet Gynecol* 2014; **211**: 7-14 [PMID: 24316272 DOI: 10.1016/j.ajog.2013.12.002]
- 3 **Romano M**, Cacciatore A, Giordano R, La Rosa B. Postpartum period: three distinct but continuous phases. *J Prenat Med* 2010; **4**: 22-25 [PMID: 22439056]
- 4 **Brenner H**, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* 2007; **56**: 1585-1589 [PMID: 17591622 DOI: 10.1136/gut.2007.122739]
- 5 **Bernstein MA**, Madoff RD, Caushaj PF. Colon and rectal cancer in pregnancy. *Dis Colon Rectum* 1993; **36**: 172-178 [PMID: 8425421]
- 6 **Toosi M**, Moaddabshoar L, Malek-Hosseini SA, Sasani MR, Mokhtari M, Mohammadianpanah M. Rectal cancer in pregnancy: a diagnostic and therapeutic challenge. *J Egypt Natl Canc Inst* 2014; **26**: 175-179 [PMID: 25150133 DOI: 10.1016/j.jnci.2014.03.003]
- 7 **Khodaverdi S**, Kord Valeshabad A, Khodaverdi M. A Case of Colorectal Cancer during Pregnancy: A Brief Review of the Literature. *Case Rep Obstet Gynecol* 2013; **2013**: 626393 [PMID: 23401815 DOI: 10.1155/2013/626393]
- 8 **Aytac E**, Ozuner G, Isik O, Gorgun E, Remzi FH. Surgical management of patients with ulcerative colitis during pregnancy: maternal and fetal outcomes. *J Crohns Colitis* 2015; **9**: 82-85 [PMID: 25518046 DOI: 10.1093/ecco-jcc/jju001]
- 9 **Brown JJ**, Wilson C, Coleman S, Joypaul BV. Appendicitis in pregnancy: an ongoing diagnostic dilemma. *Colorectal Dis* 2009; **11**: 116-122 [PMID: 18513191 DOI: 10.1111/j.1463-1318.2008.01594.x]
- 10 **Wang PI**, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, Goodsitt MM. Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations. *AJR Am J Roentgenol* 2012; **198**: 778-784 [PMID: 22451541 DOI: 10.2214/AJR.11.7405]
- 11 **Walker HG**, Al Samaraee A, Mills SJ, Kalbassi MR. Laparoscopic appendectomy in pregnancy: a systematic review of the published evidence. *Int J Surg* 2014; **12**: 1235-1241 [PMID: 25219891 DOI: 10.1016/j.ijsu.2014.08.406]
- 12 **Yaghoobi M**, Koren G, Nulman I. Challenges to diagnosing colorectal cancer during pregnancy. *Can Fam Physician* 2009; **55**: 881-885 [PMID: 19752253]
- 13 **Qureshi WA**, Rajan E, Adler DG, Davila RE, Hirota WK, Jacobson BC, Leighton JA, Zuckerman MJ, Hambrick RD, Fanelli RD, Baron T, Faigel DO. ASGE Guideline: Guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2005; **61**: 357-362 [PMID: 15758903 DOI: 10.1016/S0016-5107(04)02780-4]
- 14 **Lolis ED**, Likoudis P, Voiniadis P, Hassiakos D, Samanides L. Synchronous rectal and colon cancer caused by familial polyposis coli during pregnancy. *J Obstet Gynaecol Res* 2007; **33**: 199-202 [PMID: 17441896 DOI: 10.1111/j.1447-0756.2007.00510.x]
- 15 **Peccatori FA**, Azim HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, Pentheroudakis G. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** Suppl 6: vi160-vi170 [PMID: 23813932 DOI: 10.1093/annonc/mdt199]
- 16 **Azim HA**, Peccatori FA, Pavlidis N. Treatment of the pregnant

mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: Solid tumors. *Cancer Treat Rev* 2010; **36**: 101-109 [PMID: 20015593 DOI: 10.1016/j.ctrv.2009.11.007]

- 17 **Amant F**, Van Calsteren K, Halaska MJ, Gziri MM, Hui W, Lagae L, Willemsen MA, Kapusta L, Van Calster B, Wouters H, Heyns L, Han SN, Tomek V, Mertens L, Ottevanger PB. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. *Lancet*

*Oncol* 2012; **13**: 256-264 [PMID: 22326925 DOI: 10.1016/S1470-2045(11)70363-1]

- 18 **Litton JK**, Hodge S, Mattair D, Ramirez MM, Morrow PKH, Gonzalez-Angulo AM, Barnett CM, Hortobagyi GN, Theriault RL. Outcomes of children exposed to chemotherapy in utero for breast cancer. *J Clin Oncol* 2011; **29**: Abstr 1099
- 19 **Walsh C**, Fazio VW. Cancer of the colon, rectum, and anus during pregnancy. The surgeon's perspective. *Gastroenterol Clin North Am* 1998; **27**: 257-267 [PMID: 9546093]

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## Retrospective Study

# Prognostic value of inflammation-based markers in patients with pancreatic cancer administered gemcitabine and erlotinib

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**Author contributions:** Lee HS designed the study; Lee JM and Hyun JJ modified the study methods and performed the study; Choi HS and Kim ES collected the data; Seo YS and Jeon YT analyzed the data; Lee JM wrote the draft; Keum B, Chun HJ, Um SH and Kim CD revised the draft; Lee HS corrected the final draft and approved the manuscript.

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## Abstract

**AIM:** To evaluate the value of systemic inflammation-based markers as prognostic factors for advanced pancreatic cancer (PC).

**METHODS:** Data from 82 patients who underwent combination chemotherapy with gemcitabine and erlotinib for PC from 2011 to 2014 were collected retrospectively. Data that included the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio, and the C-reactive protein (CRP)-to-albumin (CRP/Alb) ratio were analyzed. Kaplan-Meier curves, and univariate and multivariate Cox proportional hazards regression analyses were used to identify the prognostic factors associated with progression-free survival (PFS) and overall survival (OS).

**RESULTS:** The univariate analysis demonstrated the prognostic value of the NLR ( $P = 0.049$ ) and the CRP/Alb ratio ( $P = 0.047$ ) in relation to PFS, and a positive

relationship between an increase in inflammation-based markers and a poor prognosis in relation to OS. The multivariate analysis determined that an increased NLR (hazard ratio = 2.76, 95%CI: 1.33-5.75,  $P = 0.007$ ) is an independent prognostic factor for poor OS. There was no association between the PLR and the patients' prognoses in those who had received chemotherapy that comprised gemcitabine and erlotinib in combination. The Kaplan-Meier method and the log-rank test determined significantly worse outcomes in relation to PFS and OS in patients with an NLR > 5 or a CRP/Alb ratio > 5.

**CONCLUSION:** Systemic inflammation-based markers, including increases in the NLR and the CRP/Alb ratio, may be useful for predicting PC prognoses.

**Key words:** Pancreatic cancer; Neutrophil-to-lymphocyte ratio; C-reactive protein; Albumin; Prognostic factor

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**Core tip:** This retrospective study validates the value of systemic inflammation-based markers as prognostic factors for pancreatic cancer (PC). The neutrophil-to-lymphocyte ratio and the C-reactive protein-to-albumin ratio, which can be determined from routine blood tests before chemotherapy, can be used as useful biomarkers in PC to predict a patient's response to chemotherapy.

Lee JM, Lee HS, Hyun JJ, Choi HS, Kim ES, Keum B, Seo YS, Jeon YT, Chun HJ, Um SH, Kim CD. Prognostic value of inflammation-based markers in patients with pancreatic cancer administered gemcitabine and erlotinib. *World J Gastrointest Oncol* 2016; 8(7): 555-562 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v8/i7/555.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v8.i7.555>

## INTRODUCTION

Pancreatic cancer (PC) is a devastating malignant tumor that has a poor prognosis<sup>[1]</sup>. Although surgical resection offers a good prognosis and prolongs survival, only 10%-20% of patients are eligible for a curative resection at the time of diagnosis<sup>[2,3]</sup>. Systemic chemotherapy is a major treatment modality for unresectable PC, and the National Comprehensive Cancer Network recommends gemcitabine-based chemotherapy as standard therapy for advanced or metastatic PC. The findings from recent studies have demonstrated that gemcitabine and erlotinib (Tarceva®) administered in combination improve therapeutic response rates and overall survival (OS)<sup>[4-6]</sup>. However, the PC prognosis remains extremely poor, and it is difficult to predict in advanced PC before chemotherapy. Hence, to administer effective treatment, better prognostic predictors are required than those that are currently available.

Evidence is accumulating that supports the relationship between the inflammatory response and cancer development<sup>[7,8]</sup>. Bhatti *et al.*<sup>[9]</sup> proposed that hematologic inflammation-based markers could be used as prognostic markers in resectable PC. C-reactive protein (CRP) levels, and leukocyte, neutrophil, lymphocyte, and platelet counts, as well as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), could be prognostic markers for patients with PC<sup>[10,11]</sup>. Recently, an increase in the CRP/albumin (CRP/Alb) ratio has been reported to correlate with poor prognoses in patients with malignant tumors<sup>[12-14]</sup>. However, the relationship between the CRP/Alb ratio and the PC prognosis has not been studied. Since cancer progression depends on the systemic inflammatory response<sup>[15]</sup>, we hypothesized that the status of the peripheral blood at the time of diagnosis reflects the inflammatory response and the disease activity associated with PC.

This study aimed to evaluate the prognostic value of systemic inflammation-based markers within the peripheral blood of patients with advanced or metastatic PC, and to determine their usefulness in predicting patients' responses to chemotherapy.

## MATERIALS AND METHODS

### Patients and study design

We retrospectively collected data from patients with PC who were admitted to two tertiary hospitals, namely, Anam Hospital and Ansan Hospital in South Korea, between January 2011 and December 2014. Only consecutive patients with primary PC were included in the study. All of the patients met the following criteria: (1) the presence of a pathologically confirmed pancreatic adenocarcinoma; (2) receipt of first-line chemotherapy comprising gemcitabine and erlotinib administered in combination; and (3) the presence of locally advanced or metastatic PC. Gemcitabine was administered at 1000 mg/m<sup>2</sup> three times per week, which was followed by rest for 1 wk. Erlotinib was administered as a single oral 150 mg dose during chemotherapy. Patients who had undergone previous curative resections of their primary pancreatic tumors, or who had undergone first-line chemotherapy that involved other chemotherapeutic agents, including 5-fluorouracil, were excluded from this study.

The patients' demographic, clinical, and laboratory data, including the WBC and differential counts, the platelet count, and information about tumor markers, were collected and analyzed. All of the laboratory data were obtained on the day of or on the day that followed hospital admission. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count. The CRP/Alb ratio was determined as the CRP level divided by the serum albumin level. The follow-up duration was defined as the period from the first day of treatment to the day of death or August 2015.



**Table 1 Patient demographics and laboratory findings**

Characteristic	
No. of patients, <i>n</i>	82
Age, mean $\pm$ SD, yr	63.5 $\pm$ 10.7
Male, <i>n</i> (%)	49 (60)
Laboratory findings	
WBC count, mean $\pm$ SD	6259 $\pm$ 2667
Platelet count, mean $\pm$ SD, $\times$ 1000	225 $\pm$ 94
Neutrophil count, mean $\pm$ SD	4175 $\pm$ 2139
Lymphocyte count, mean $\pm$ SD	1462 $\pm$ 729
CRP, mean $\pm$ SD, mg/dL	12.5 $\pm$ 23.8
Albumin, mean $\pm$ SD, g/dL	3.5 $\pm$ 0.6
CA19-9, median, IU/mL	503.8
CEA, median, ng/mL	2.8
ECOG performance status score, <i>n</i> (%)	
0	22 (27)
1	48 (58)
2	12 (15)
Inflammatory markers	
NLR, median, range	3.1 (1-48)
PLR, median, range	141 (44-921)
CRP/albumin ratio, median, range	0.5 (0-37.7)
Staging	
Locally advanced, <i>n</i> (%)	14 (17)
Metastatic, <i>n</i> (%)	68 (83)

WBC: White blood cell; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ECOG: Eastern Cooperative Oncology Group.

### Statistical analysis

An increased NLR was defined as  $> 5$ , and an increased PLR was defined as  $> 150$ <sup>[14]</sup>. The CRP/Alb ratio cutoff value was 0.5, which was based on a previous study<sup>[13]</sup>. Progression was defined as a 25% or more increase in total tumor size and/or the appearance of new lesions at any site. Progression-free survival (PFS) was defined as the time from treatment to the first observation of progression. OS was defined as the date of the first treatment to the date of death. The Kaplan-Meier method and the log-rank test were used to compare the PFS and OS rates, and the 95%CI were calculated. The univariate and multivariate analyses were carried out using the Cox proportional hazards model, and student's *t*-test was used to analyze the response and survival time results. A *P* value  $< 0.05$  was considered statistically significant. The statistical analyses were conducted using IBM® SPSS® software version 20.0 (IBM Corporation, Armonk, NY, United States).

## RESULTS

### Patient characteristics

Table 1 presents the characteristics of the 82 patients who met all of the study's eligibility criteria. The mean age of the patients when they were diagnosed with PC was  $63.5 \pm 10.7$  years, and 60% of the patients were men. Most of the patients (85%) had favorable performance statuses with Eastern Cooperative Oncology Group (ECOG) scores of 0 or 1. The median values for the inflammatory

**Table 2 Univariate analysis of the clinical parameters for the prediction of progression-free survival**

Parameter	<i>n</i>	Univariate analysis	
		HR (95%CI)	<i>P</i> value
Sex			
Woman	33	1	
Man	49	1.37 (0.82-2.3)	0.232
Age (yr)			
$< 65$	41	1	
$\geq 65$	41	0.85 (0.52-1.41)	0.536
Staging			
Locally advanced	14	1	
Metastatic	68	1.39 (0.68-2.82)	0.367
ECOG performance status score			
0-1	70	1	
2	12	1.49 (0.77-2.87)	0.234
CA19-9 (IU/mL)			
$< 1000$	48	1	
$\geq 1000$	34	1.33 (0.81-2.21)	0.264
CEA (ng/mL)			
$< 5$	46	1	
$\geq 5$	29	1.24 (0.72-2.13)	0.441
NLR			
$\leq 5$	62	1	
$> 5$	20	1.80 (1.04-3.19)	0.049
PLR			
$\leq 150$	46	1	
$> 150$	36	1.22 (0.73-2.02)	0.448
CRP/albumin ratio			
$\leq 0.5$	42	1	
$> 0.5$	40	1.72 (1.07-2.80)	0.047

ECOG: Eastern Cooperative Oncology Group; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CRP: C-reactive protein; HR: Hazard ratio.

markers were as follows: NLR: 3.1 (range, 1-48); PLR: 141 (range, 44-921); and CRP/Alb ratio: 0.5 (range, 0-38). All of the patients were finally diagnosed with pancreatic adenocarcinoma based on pathologic examinations. Fourteen patients (17%) had locally advanced PC and 68 patients (83%) had metastatic lesions when they were diagnosed with PC.

### Prognostic value of the factors associated with PC

Univariate analyses were performed using sex, age, the tumor stage, the ECOG performance status score, the tumor markers, and the inflammatory markers as possible variables for PFS (Table 2), and it determined that an NLR  $> 5$  ( $P = 0.049$ ) and a CRP/Alb ratio  $> 0.5$  ( $P = 0.047$ ) were significant predictors of a poor prognosis. Univariate and multivariate analyses were also performed in relation to OS (Table 3). The univariate analysis revealed that the presence of distant metastasis ( $P = 0.017$ ), an ECOG performance status score of 2 ( $P = 0.002$ ), an NLR  $> 5$  ( $P = 0.008$ ), and a CRP/Alb ratio  $> 0.5$  ( $P = 0.011$ ) were significantly associated with poor OS. The multivariate analysis showed that an ECOG performance status score of 2 [hazard ratio (HR) = 2.94, 95%CI: 1.42-6.08,  $P = 0.004$ ] and an NLR  $> 5$  (HR = 2.76, 95%CI: 1.33-5.75,

**Table 3** Univariate and multivariate analysis of the clinical parameters for the prediction of overall survival

Parameter	n	Univariate analysis		Multivariate analysis	
		HR (95%CI)	P value	HR (95%CI)	P value
Sex					
Woman	33	1			
Man	49	1.26 (0.73-2.17)	0.418		
Age (yr)					
≥ 65	41	1			
< 65	41	1.27 (0.75-2.17)	0.379		
Staging					
Locally advanced	14	1		1	
Metastatic	68	2.87 (1.20-6.83)	0.017	2.10 (0.85-5.18)	0.108
ECOG performance status score					
0-1	70	1		1	
2	12	2.96 (1.49-5.89)	0.002	2.94 (1.42-6.08)	0.004
CA19-9 (IU/mL)					
< 1000	48	1			
≥ 1000	34	1.45 (0.79-2.66)	0.224		
CEA (ng/mL)					
< 5	46	1			
≥ 5	29	1.67 (0.90-3.10)	0.107		
NLR					
≤ 5	62	1		1	
> 5	20	2.61 (1.29-5.27)	0.008	2.76 (1.33-5.75)	0.007
PLR					
≤ 150	46	1			
> 150	36	1.43 (0.79-2.60)	0.24		
CRP/albumin					
≤ 0.5	42	1		1	
> 0.5	40	2.13 (1.19-3.81)	0.011	1.60 (0.84-3.04)	0.151

ECOG: Eastern Cooperative Oncology Group; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CRP: C-reactive protein; HR: Hazard ratio.

$P = 0.007$ ) were independent factors associated with the prognosis of PC.

#### Inflammation-based factors and PC outcomes

By the time this study was completed, 57 patients had died because of disease progression. The patients were categorized according to the NLR and the CRP/Alb ratio and subgroup analyses were performed. The groups were compared with respect to the duration of chemotherapy and the time until death (Table 4). Patients with initial NLRs  $\leq 5$  continued chemotherapy with gemcitabine and erlotinib for longer. The time to disease progression was significantly longer when the patients' NLRs did not increase. The mean time until death was longer in patients who had NLRs  $\leq 5$  compared with patients who had NLRs  $> 5$ . The mean time until death was shorter in patients with CRP/Alb ratios  $> 0.5$  compared with patients with CRP/Alb ratios  $\leq 0.5$ .

#### Prognostic comparisons based on the NLR and the CRP-to-albumin ratio

The NLR has been identified as a prognostic indicator in patients with PC who are undergoing gemcitabine-based chemotherapy; therefore, we compared the cancer prognosis in a group of patients with NLR  $\leq 5$  with that in a group of patients with NLR  $> 5$ . Kaplan-Meier analyses determined that PFS was significantly better in patients

with NLRs  $\leq 5$  ( $4.9 \pm 0.5$  mo) compared with those with NLRs  $> 5$  ( $3.1 \pm 0.7$  mo) ( $P = 0.043$ ) (Figure 1A), and that OS was significantly better in patients with NLRs  $\leq 5$  ( $11.1 \pm 1.2$  mo) compared with those with NLRs  $> 5$  ( $5.8 \pm 0.9$  mo) ( $P = 0.005$ ) (Figure 1B). PFS for patients with CRP/Alb ratios  $> 0.5$  ( $3.2 \pm 0.4$  mo) was significantly worse compared with those with CRP/Alb ratios  $\leq 5$  ( $5.3 \pm 0.7$  mo) ( $P = 0.034$ ) (Figure 2A), and OS for patients with CRP/Alb ratios  $> 0.5$  ( $7.9 \pm 1.2$  mo) was significantly worse compared with those with CRP/Alb ratios  $\leq 5$  ( $12.7 \pm 1.2$  mo) ( $P = 0.007$ ) (Figure 2B).

## DISCUSSION

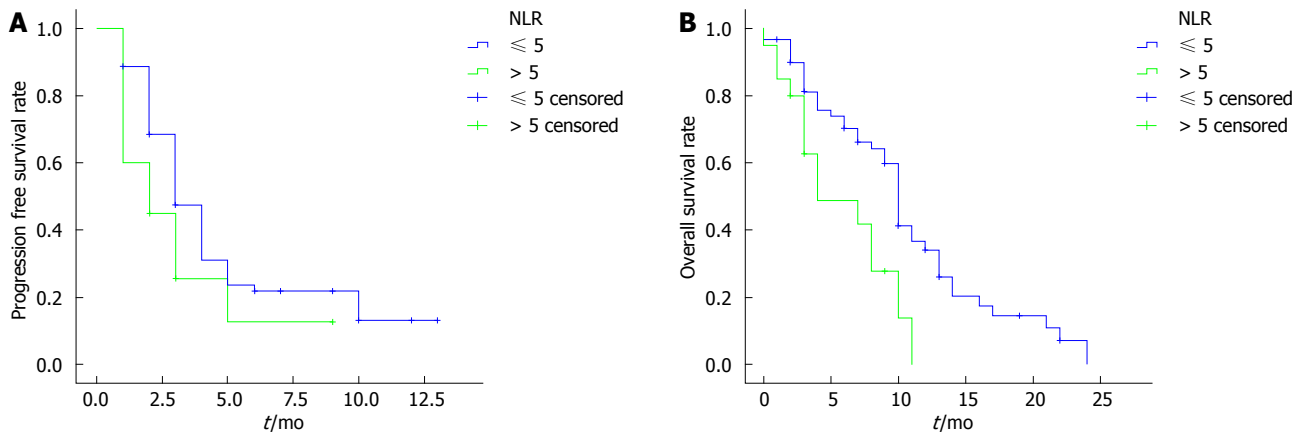
Systemic chemotherapy is recommended as palliative therapy for PC<sup>[16]</sup>, but only a limited number of patients benefit from chemotherapy. Gemcitabine-based combination therapy is considered an effective first-line treatment for advanced PC<sup>[4,17-19]</sup>. While the tumor stage and the carbohydrate antigen 19-9 levels have been used to predict patients' prognoses<sup>[20-22]</sup>, predicting the therapeutic effect of or a patient's response to chemotherapy is difficult.

Findings from recent studies of different malignant tumors have suggested that increases in the levels of systemic inflammation are indicative of poor survival<sup>[23,24]</sup>. Inflammatory cells within the tumor microenvironment play important roles in tumor development and in the

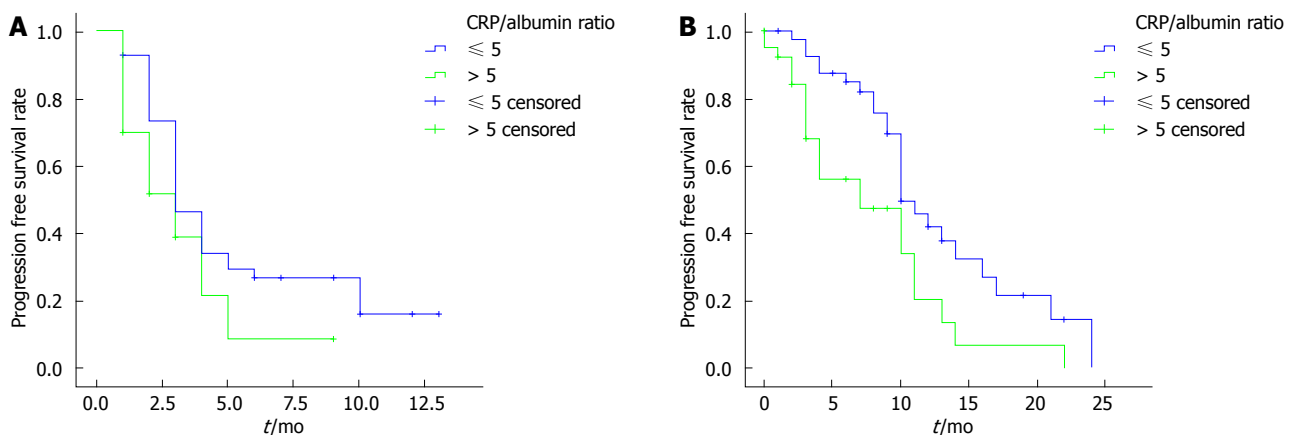
**Table 4** Mean times to disease progression and death according to the neutrophil-to-lymphocyte ratio and the C-reactive protein/albumin ratio

Variable	NLR $\leq 5$	NLR $> 5$	<i>P</i> value	CRP/albumin ratio $\leq 0.5$	CRP/albumin ratio $> 0.5$	<i>P</i> value
Time until disease progression, mean $\pm$ SD, mo	3.0 $\pm$ 1.7	1.9 $\pm$ 1.2	0.016	3.0 $\pm$ 1.8	2.3 $\pm$ 1.4	0.08
Time until death, mean $\pm$ SD, mo	9.3 $\pm$ 5.9	4.7 $\pm$ 3.5	0.014	10.0 $\pm$ 5.4	6.0 $\pm$ 5.5	0.01

NLR: Neutrophil-to-lymphocyte ratio; CRP: C-reactive protein.



**Figure 1** Kaplan-Meier curves for progression-free survival and overall survival according to the neutrophil-lymphocyte ratio. A: PFS stratified according to the NLR; B: Overall survival stratified according to the NLR. NLR: Neutrophil-to-lymphocyte ratio; PFS: Progression-free survival.



**Figure 2** Kaplan-Meier curves for progression-free survival and overall survival according to the C-reactive protein /albumin ratio. A: Progression-free survival stratified according to the CRP/albumin ratio; B: Overall survival stratified according to the CRP/albumin ratio. CRP: C-reactive protein.

survival of malignant cells<sup>[25,26]</sup>. Therefore, systemic inflammation-based markers may be indicators of cancer prognosis and of patients' responses to therapy. Since these markers can be readily measured in peripheral blood samples, its usefulness would be greatly expectable in practice. Indeed, some investigators have described the prognostic value of these systemic inflammatory response markers in advanced PC<sup>[11,27-29]</sup>.

The current investigation scrutinized the value of a number of clinical parameters, including the NLR, PLR, and the CRP/Alb ratio, as prognostic predictors in patients with PC who received combination chemotherapy that comprised gemcitabine and erlotinib. The univariate and multivariate analyses determined that a higher

ECOG performance status score, metastatic disease, a higher NLR, and a higher CRP/Alb ratio were associated with poor outcomes. A multivariate analysis of the significant inflammation-related factors determined that the NLR was independently associated with OS. In the patients with PC, a higher NLR was associated with significantly worse OS (2.6 mo) compared with a lower NLR (8.5 mo), but the PLR was not determined to be an independent prognostic factor. A higher CRP/Alb ratio was associated with a poor prognosis according to the univariate analysis, but the multivariate analysis did not show that it was an independent prognostic factor.

The mechanism that underlies the association between inflammation-based markers and poor PC outcomes

has not been clarified. Systemic inflammatory changes would be reflected in increases in the neutrophil levels, and these could be induced by tumor invasion and disease progression, despite the administration of chemotherapy. Inflammatory responses can inhibit the immune system by suppressing the cytolytic activity of the immune cells, including that associated with the lymphocytes, activated T cells, and natural killer cells<sup>[30]</sup>. Furthermore, inflammatory responses can promote tumor angiogenesis, invasion, and metastasis by recruiting regulatory T lymphocytes and activating cytokine production<sup>[31,32]</sup>. Since an increase in the neutrophil count or a decrease in the lymphocyte count within the WBC count will present as a higher NLR, the NLR will be strongly associated with the prognosis for a patient with a malignant tumor. Moreover, cancer progression against chemotherapy activates inflammatory processes within the tumor microenvironment<sup>[33]</sup>, and the WBC ratios may change under these conditions.

The prognostic value of the preoperative NLR has been described in patients with resectable PC<sup>[34-36]</sup>, but the response of the NLR to chemotherapy and its value as a prognostic marker have not been established. We observed that the mean times until disease progression or death were significantly shorter in patients with NLRs > 5 compared with those whose NLRs were not elevated. Elevated neutrophil counts may aid cancer progression by providing a favorable environment for tumor growth. Furthermore, lymphocytopenia, which can be induced by many of the inhibitory immunologic mediators that are released by tumor cells, results in a weakened immune system that would contribute to poor patient outcomes during systemic chemotherapy.

To the best of our knowledge, this is the first study to evaluate the value of the CRP/Alb ratio in advanced PC. Another strength of our study is that the data were only collected from patients who were receiving a unified chemotherapy regimen that comprised gemcitabine and erlotinib. While other studies of PC have included both resectable and unresectable tumors<sup>[9,37]</sup>, we excluded patients with PC who had undergone surgery from the analysis. However, there are several limitations to our study. First, this was a retrospective study that involved a relatively small number of patients. While an elevated NLR was related to the PC prognosis, we could not validate the prognostic value of the PLR in this study. More data obtained from larger numbers of patients will be required to determine the true value of the PLR for predicting PC prognoses. Second, while we excluded those patients who had been diagnosed with acute pancreatitis or other infections, patients with early infections may have been included during the selection process. Since pancreatic duct obstruction and biliary tract invasion are relatively frequent in PC, patients with potentially aggressive disease may have been allocated to the group containing patients with higher NLRs. Finally, this study only evaluated patients who received combination chemotherapy with gemcitabine and erlotinib; hence, it is difficult to extrapolate the data to

all patients with PC. The therapeutic strategy for PC may differ considerably in relation to a patient's socioeconomic status, comorbidities, and other factors. However, since gemcitabine-based chemotherapy is widely recommended as first-line palliative chemotherapy for PC throughout the world, the NLR, which is easily calculated, would assist clinicians to predict patients' therapeutic responses and PC prognoses.

In summary, our results strongly support the idea that systemic inflammation-based parameters may be useful prognostic markers for patients with advanced PC. The NLR when determined at the time of a diagnosis of PC could be a valuable marker for predicting a patient's response to chemotherapy with gemcitabine and erlotinib. Furthermore, the CRP/Alb ratio may be valuable as a prognostic factor in PC. More prospective studies are needed to verify the usefulness of these inflammation-based markers in patients with PC.

## COMMENTS

### Background

Inflammation based markers have been known to have a prognostic value predicting the outcome of various cancers. Since the status of the peripheral blood reflects the inflammatory response at the time of diagnosis, it could be used the systemic inflammation based markers [neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, C-reactive protein (CRP)-to-albumin ratio, etc.] as a prognostic biomarker in advanced pancreatic cancer (PC).

### Research frontiers

It is important to be able to predict the outcome and response to chemotherapy in advanced PC. This study assessed the prognostic value of systemic inflammation based markers in patients with palliative chemotherapy due to inoperable PC.

### Innovations and breakthroughs

Although prior investigators had studied about the prognostic value of NLR in malignancy, there was no study about the CRP-to-albumin ratio in PC. The present study showed that both NLR and CRP-to-albumin ratio can be useful and easy biomarkers to predict the response and outcome of PC.

### Applications

It can be easily calculated NLR or CRP-to-albumin ratio from routine blood tests. The systemic inflammation-based markers can be useful tool to predict the outcome in patients with PC.

### Terminology

The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count. The CRP/Alb ratio was determined as the CRP level divided by the serum albumin level.

### Peer-review

The manuscript by Lee *et al* aims to identify inflammation-based markers in patients with pancreatic cancer treated with gemcitabine and erlotinib. Eighty-two pancreatic cancer patients were enrolled in this retrospective study. Patients received combination chemotherapy with gemcitabine and erlotinib. Multivariate analysis demonstrated that an increased neutrophil-to-lymphocyte ratio (hazard ratio = 2.76, 95%CI: 1.33-5.75,  $P = 0.007$ ) was an independent prognostic factor for poor overall survival. CRP/albumin ratio was related to progression free survival. The manuscript is in general well written and the topic is of interest.



## REFERENCES

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]
- 2 Ferrone CR, Pieretti-Vanmarcke R, Bloom JP, Zheng H, Szymonifka J, Wargo JA, Thayer SP, Lauwers GY, Deshpande V, Mino-Kenudson M, Fernández-del Castillo C, Lillmoore KD, Warshaw AL. Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. *Surgery* 2012; **152**: S43-S49 [PMID: 22763261 DOI: 10.1016/j.surg.2012.05.020]
- 3 Stathis A, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. *Nat Rev Clin Oncol* 2010; **7**: 163-172 [PMID: 20101258 DOI: 10.1038/nrclinonc.2009.236]
- 4 Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]
- 5 Yang ZY, Yuan JQ, Di MY, Zheng DY, Chen JZ, Ding H, Wu XY, Huang YF, Mao C, Tang JL. Gemcitabine plus erlotinib for advanced pancreatic cancer: a systematic review with meta-analysis. *PLoS One* 2013; **8**: e57528 [PMID: 23472089 DOI: 10.1371/journal.pone.0057528]
- 6 Diaz Beveridge R, Alcolea V, Aparicio J, Segura Á, García J, Corbellas M, Fonfria M, Giménez A, Montalar J. Management of advanced pancreatic cancer with gemcitabine plus erlotinib: efficacy and safety results in clinical practice. *JOP* 2014; **15**: 19-24 [PMID: 24413779 DOI: 10.6092/1590-8577/1570]
- 7 Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**: 883-899 [PMID: 20303878 DOI: 10.1016/j.cell.2010.01.025]
- 8 Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer* 2013; **13**: 759-771 [PMID: 24154716 DOI: 10.1038/nrc3611]
- 9 Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. *Am J Surg* 2010; **200**: 197-203 [PMID: 20122680 DOI: 10.1016/j.amjsurg.2009.08.041]
- 10 Bilici A. Prognostic factors related with survival in patients with pancreatic adenocarcinoma. *World J Gastroenterol* 2014; **20**: 10802-10812 [PMID: 25152583 DOI: 10.3748/wjg.v20.i31.10802]
- 11 Martin HL, Ohara K, Kiberu A, Van Hagen T, Davidson A, Khattak MA. Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer. *Intern Med J* 2014; **44**: 676-682 [PMID: 24750233 DOI: 10.1111/imj.12453]
- 12 Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, Fushiya N, Koike K, Nishino H, Matsushima M. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. *Ann Surg Oncol* 2015; **22**: 803-810 [PMID: 25190127 DOI: 10.1245/s10434-014-4048-0]
- 13 Xu XL, Yu HQ, Hu W, Song Q, Mao WM. A Novel Inflammation-Based Prognostic Score, the C-Reactive Protein/Albumin Ratio Predicts the Prognosis of Patients with Operable Esophageal Squamous Cell Carcinoma. *PLoS One* 2015; **10**: e0138657 [PMID: 26390126 DOI: 10.1371/journal.pone.0138657]
- 14 Xue P, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, Kawaguchi Y, Takaori K, Matsumoto S, Uemoto S, Chiba T. Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. *Cancer Med* 2014; **3**: 406-415 [PMID: 24519894 DOI: 10.1002/cam4.204]
- 15 Borsig L, Wolf MJ, Roblek M, Lorentzen A, Heikenwalder M. Inflammatory chemokines and metastasis--tracing the accessory. *Oncogene* 2014; **33**: 3217-3224 [PMID: 23851506 DOI: 10.1038/onc.2013.272]
- 16 Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, Ghaneh P. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer* 2007; **96**: 1183-1190 [PMID: 17406358 DOI: 10.1038/sj.bjc.6603719]
- 17 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Stormiolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413 [PMID: 9196156]
- 18 Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008; **8**: 82 [PMID: 18373843 DOI: 10.1186/1471-2407-8-82]
- 19 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjuland SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]
- 20 Eloubeidi MA, Desmond RA, Wilcox CM, Wilson RJ, Manchikalapati P, Fouad MM, Eltoum I, Vickers SM. Prognostic factors for survival in pancreatic cancer: a population-based study. *Am J Surg* 2006; **192**: 322-329 [PMID: 16920426 DOI: 10.1016/j.amjsurg.2006.02.017]
- 21 Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, Colvin EK, Nagrial A, Chin VT, Chantrell LA, Samra JS, Gill AJ, Kench JG, Merrett ND, Das A, Musgrove EA, Sutherland RL, Biankin AV. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol* 2012; **23**: 1713-1722 [PMID: 22241899 DOI: 10.1093/annonc/mdr561]
- 22 Balleaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012; **3**: 105-119 [PMID: 22811878 DOI: 10.3978/j.issn.2078-6891.2011.021]
- 23 Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, Wang T, Zhu W, Liu P. Prognostic value of PLR in various cancers: a meta-analysis. *PLoS One* 2014; **9**: e101119 [PMID: 24968121 DOI: 10.1371/journal.pone.0101119]
- 24 Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014; **15**: e493-e503 [PMID: 25281468 DOI: 10.1016/S1470-2045(14)70263-3]
- 25 Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. *Oncogene* 2008; **27**: 5904-5912 [PMID: 18836471 DOI: 10.1038/onc.2008.271]
- 26 Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009; **30**: 1073-1081 [PMID: 19468060 DOI: 10.1093/carcin/bgp127]
- 27 An X, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, He YJ, Xu RH, Jiang WQ. Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. *Biomarkers* 2010; **15**: 516-522 [PMID: 20602543 DOI: 10.3109/1354750X.2010.491557]
- 28 Teo M, Mohd Shari MS, McDonnell F, Conlon KC, Ridgway PF, McDermott RS. Prognostic role of neutrophil-to-lymphocyte ratio in advanced pancreatic ductal adenocarcinoma: impact of baseline fluctuation and changes during chemotherapy. *Tumori* 2013; **99**: 516-522 [PMID: 24326841 DOI: 10.1700/1361.15104]
- 29 Luo G, Guo M, Liu Z, Xiao Z, Jin K, Long J, Liu L, Liu C, Xu J, Ni Q, Yu X. Blood neutrophil-lymphocyte ratio predicts survival in patients with advanced pancreatic cancer treated with chemotherapy. *Ann Surg Oncol* 2015; **22**: 670-676 [PMID: 25155401 DOI: 10.1245/s10434-014-4021-y]
- 30 el-Hag A, Clark RA. Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. *J Immunol* 1987; **139**: 2406-2413 [PMID: 2821114]
- 31 Germano G, Allavena P, Mantovani A. Cytokines as a key component of cancer-related inflammation. *Cytokine* 2008; **43**:



- 32 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]
- 33 **Quail DF**, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med* 2013; **19**: 1423-1437 [PMID: 24202395 DOI: 10.1038/nm.3394]
- 34 **Stotz M**, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, Kornprat P, AlZoughbi W, Seggewies FS, Lackner C, Stojakovic T, Samonigg H, Hoefler G, Pichler M. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer* 2013; **109**: 416-421 [PMID: 23799847 DOI: 10.1038/bjc.2013.332]
- 35 **Aliustaoglu M**, Bilici A, Seker M, Dane F, Gocun M, Konya V, Ustaalioglu BB, Gumus M. The association of pre-treatment peripheral blood markers with survival in patients with pancreatic cancer. *Hepatogastroenterology* 2010; **57**: 640-645 [PMID: 20698242]
- 36 **Smith RA**, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg* 2009; **197**: 466-472 [PMID: 18639229 DOI: 10.1016/j.amjsurg.2007.12.057]
- 37 **Yang JJ**, Hu ZG, Shi WX, Deng T, He SQ, Yuan SG. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. *World J Gastroenterol* 2015; **21**: 2807-2815 [PMID: 25759553 DOI: 10.3748/wjg.v21.i9.2807]

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## Observational Study

# Undernutrition, risk of malnutrition and obesity in gastroenterological patients: A multicenter study

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## Abstract

**AIM:** To investigate the prevalence of undernutrition, risk of malnutrition and obesity in the Italian gastroenterological population.

**METHODS:** The Italian Hospital Gastroenterology Association conducted an observational, cross-sectional multicenter study. Weight, weight loss, and body mass index were evaluated. Undernutrition was defined as unintentional weight loss > 10% in the last three-six months. Values of Malnutrition Universal Screening Tool (MUST) > 2, NRS-2002 > 3, and Mini Nutritional Assessment (MNA) from 17 to 25 identified risk of malnutrition in outpatients, inpatients and elderly patients, respectively. A body mass index  $\geq 30$  indicated obesity. Gastrointestinal pathologies were categorized into acute, chronic and neoplastic diseases.

**RESULTS:** A total of 513 patients participated in the study. The prevalence of undernutrition was 4.6% in outpatients and 19.6% in inpatients. Moreover, undernutrition was present in 4.3% of the gastrointestinal patients with chronic disease, 11.0% of those with acute disease, and 17.6% of those with cancer. The risk of malnutrition increased progressively and significantly in chronic, acute and neoplastic gastrointestinal diseases in inpatients and the elderly population. Logistical regression analysis confirmed that cancer was a risk factor for undernutrition (OR = 2.7; 95%CI: 1.2-6.44,  $P = 0.02$ ). Obesity and overweight were more frequent in outpatients.

**CONCLUSION:** More than 63% of outpatients and 80% of inpatients in gastroenterological centers suffered from significant changes in body composition and required specific nutritional competence and treatment.

**Key words:** Obesity; Malnutrition; Risk of Malnutrition; NRS2002; Gastrointestinal disease

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**Core tip:** The relevance of this study concerns the finding that in patients with gastroenterological disease, both prevalence of undernutrition and risk of malnutrition were higher in patients admitted to the hospital and in patients with cancer disease, while obesity and overweight were more frequently detected in outpatients. In conclusion, we can attest that two-thirds of gastroenterological patients suffered from abnormalities in body composition and required targeted nutritional treatments.

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## INTRODUCTION

Malnutrition is defined as a structural and functional alteration of the body composition. Although the term malnutrition is commonly used in the sense of undernutrition, it encompasses both weight loss (undernutrition) and weight gain (overweight and obesity). The physiological basis of undernutrition and obesity is the deficit (undernutrition) or the excess (obesity) of calories that results in measurable adverse effects on clinical outcomes<sup>[1-5]</sup>. The equilibrium between the total energy requirements, nutrient intake and utilization is mediated by hormonal and cytokine stimuli that induce the activation of intracellular metabolic pathways.

Previous papers have found that the prevalence of hospital undernutrition varies between 27% to more than 50% depending on the identification criteria, the medical or surgical setting and the age of the patients<sup>[6-10]</sup>.

It is important to identify and treat undernutrition because it has been associated with a higher likelihood of hospitalization, a prolonged (by 29%-65%) hospital stay<sup>[11-15]</sup> and an increase in costs of up to 68%<sup>[16,17]</sup>. Moreover, it must be emphasized that hospital undernutrition worsens if untreated<sup>[18]</sup>. Today, many health care workers do not recognize malnutrition and do not consider nutrition as one of the more relevant aspects of the clinical management of patients<sup>[19]</sup>.

The risk of undernutrition can be identified using different validated nutritional screening tools, such as the NRS-2002, MUST, and the MNA<sup>[20-22]</sup>.

Of note, the prevalence of overweight and obesity has been steadily growing in the general population and among inpatients and represent important risk factors of morbidity and mortality<sup>[23-27]</sup>.

Currently few data are available in the literature about the prevalence of undernutrition and the risk of malnutrition among Italian inpatients and outpatients, particularly in the gastroenterological setting. The Italian multicenter HOMIS study identified undernutrition in 19.1% and obesity in 24.8% of its patients<sup>[28]</sup>. Another Italian multicenter study, PIMAI, reported a prevalence rate of undernutrition of 30.7%, a risk of malnutrition, evaluated by the NRS-2002, of 28.6% and a rate of obesity of 21%<sup>[29,30]</sup>.

The nutritional state of Italian gastroenterological patients has been described in an Italian multicenter study<sup>[31]</sup> that involved twenty-seven gastroenterology units. The study highlighted a mean of 27% of undernourished patients with a wide range (4% to 55%), probably due to the lack of appropriate nutritional assessment.

Consistent data on the prevalence of malnutrition in gastroenterology units have been limited to a few subsets of patients such as those with cirrhosis<sup>[32-36]</sup> and Crohn's disease<sup>[37-39]</sup>.

Similarly, the prevalence of obesity in Italian gastroenterology centers has not been adequately studied, although it is an important risk factor for many gastroenterological diseases<sup>[40-42]</sup>, and it seems to affect approximately 12% of discharged patients<sup>[43]</sup>.

The aim of this study is to measure the prevalence rate of undernutrition, risk of malnutrition and obesity in the Italian gastroenterological population suffering from acute, chronic and neoplastic disease.

## MATERIALS AND METHODS

### Study design

This was an observational, cross-sectional and prospective multicenter study that was urged and supported by the Italian Hospital Gastroenterology Association (AIGO).

Nineteen Italian Gastroenterological Units and Services participated in the study, as disclosed by the AIGO website.

### Inclusion criteria

All inpatients and outpatients (day hospital and ambulatory) admitted between January 14 and 20, 2013 were consecutively enrolled in the study and submitted to nutritional assessment. As this was an observational study, the sample size was determined by the number of inpatients and outpatients who visited the various centers during the study week.

### Patient population

In this study, we enrolled three different categories of patients with gastrointestinal disease: (1) subjects with a diagnosis of acute gastrointestinal disease: Dysphagia, dyspepsia, heartburn, other abdominal pains, acute diarrhea, exacerbation of chronic diarrhea, acute constipation, digestive hemorrhage, acute hepatitis, cholangitis, rectum hemorrhage, inflammatory bowel disease (IBD) exacerbation, or acute pancreatitis; (2) patients with chronic gastroenterological disease: Reflux disease, achalasia, chronic gastritis, chronic viral hepatitis, chronic alcoholic hepatitis, non-alcoholic fatty liver disease, other chronic hepatitis, cirrhosis, chronic pancreatitis, Crohn's disease and ulcerative proctocolitis, other chronic enteropathy, or chronic constipation; and (3) patients with gastrointestinal cancer: Esophagus, gastric, small bowel, colon, pancreatic, or biliary cancer and hepatocarcinoma. Patients were categorized as having (1) chronic disease, if the symptoms, signs and diagnosis had persisted for  $\geq 6$  mo; (2) acute disease, if the symptoms, signs and diagnosis had recently appeared, regardless of the presence of chronic disease; or (3) cancer, if affected by gastroenterological neoplastic disease, regardless of the presence of acute and/or chronic disease, as it was assumed that the presence of neoplastic disease itself was sufficient to determine further deterioration of a patient's nutritional status.

### Nutritional parameters

Weight (kg) and height (centimeters) were measured in the morning in fasting patients dressed in their underwear and without shoes.

The body mass index (BMI) was calculated by dividing the weight in kg by the square of height in meters. Weight loss was calculated as the difference between the

current weight and the weight in the last three-six months as reported by the patient. Patients were considered undernourished when they presented an unintentional (*i.e.*, without voluntary dietary restriction) weight loss  $> 10\%$  in the last 3-6 mo. Obesity was defined as a BMI  $\geq 30$ , and overweight a BMI between 25 and 29.9. Obese patients were considered undernourished when they lost more than 10% of their weight while receiving their usual diet. The risk of malnutrition was calculated using three different specific tools, as shown in Table 1.

Specifically, the calculation of the three methods are described in detail in the following text: (1) the Malnutrition Universal Screening Tool (MUST) was used for outpatients. This method was based on the BMI, the unintentional weight loss and the presence of acute disease that was able to significantly reduce nutrient intake in the following five days. The total score ranged from 0-6; a score of 0 indicated null or low risk of malnutrition, a score of 1 suggested a moderate risk of malnutrition, and a score  $\geq 2$  was indicative of a severe risk of malnutrition<sup>[44]</sup>. We considered a score  $\geq 2$  to identify patients at nutritional risk.

The Nutritional Risk Screening Score 2002 (NRS-2002) has been recommended by ESPEN to screen inpatients. This test evaluates the nutritional risk (score: 0-3) and the severity of disease (score: 0-3) with an additional point for patients  $\geq 70$  years old. The final score ranges from 1 to 7. The patient is considered at nutritional risk for scores higher than 3<sup>[45]</sup>.

The Mini Nutritional Assessment (MNA) is a tool for elderly patients ( $\geq 65$  years). This tool has two parts. The first part consists of six items and results in a score between 0 and 14; a score lower than 12 is considered indicative of risk of undernutrition and leads to the patient answering the second part of the tool, which is composed of 12 items with a possible maximal score of 16. A total score  $< 17$  is indicative of malnutrition, a score between 17 and 25 indicates risk of undernutrition, while scores  $> 25$  are indicative of well-nourished patients<sup>[46-48]</sup>.

We used the MUST and NRS-2002 to evaluate the risk of malnutrition in  $< 65$ -year-old patients and the MNA for those  $\geq 65$  years old.

### Ethical considerations

This study was designed with the aim of obtaining epidemiological data and anthropometric measurements that did not compromise patient's safety. All data were anonymous. Patients were referred using the first two letters of their name and surname and with a consecutive number.

A written informed consent statement was obtained from each patient prior to study inclusion. The study was conducted with the consensus of the local ethical committees of each center and of all the patients.

### Statistical analysis

The results were presented as the mean  $\pm$  SD. Categorical data were described as frequencies. The nonparametric Mann-Whitney *U* test was used to compare continuous

**Table 1** Subscores of the three nutritional risk screening tests used in the study

Test	Subscore			Nutritional risk score
MUST	BMI (score: 0-2)	Unintentional weight loss (score: 0-2)	Acute disease able to significantly reduce nutrient intake in the following 5 d (score: 2)	$\geq 2$
NRS-2002	Pre-test: BMI < 20.5; weight loss, reduced caloric intake, acute disease	Nutritional risk: Weight loss, BMI, caloric intake (score: 0-3)	Severity of disease (score: 0-3)	Age $\geq 70$ -yr-old (score: 1)
MNA	First part (six items: Caloric food intake, weight loss, motility, psychological stress, neuropsychological disease, BMI (score: 0-14)	If subscore $\leq 11$ : Complete second part	Second part (12 items: Home and nutritional autonomy, drugs, bedsores, daily meals, brachial and calf circumference; (maximal score of 16)	17-25

MUST: Malnutrition Universal Screening Tool; NRS: Nutritional Risk Screening; MNA: Mini Nutritional Assessment.

variables, and  $\chi^2$  test was used to compare categorical data. Two-tailed *P* values less than 0.05 were considered statistically significant.

Univariate and multivariate analyses were used to identify potential predictors of malnutrition. A linear trend test was used to assess associations with severity of disease. A stepwise backward logistical regression analysis, adjusted for age and gender and considering acute, chronic and neoplastic disease independent of each other, was performed to identify significant independent predictors of malnutrition. Statistical analyses were performed using SPSS software version 12.0 (SPSS Inc., Chicago, IL, United States).

## RESULTS

Five hundred and ninety-seven patients were enrolled. We excluded from the statistical analysis five patients for incomplete data and 79 cirrhotic patients because of the negative effects of ascites and peripheral edema on nutritional parameters.

In Table 2 we report the anthropometric and nutritional data of the 513 patients enrolled in the 19 gastroenterology units participating in the study: 51.4% were males and 48.6% females, and the average age was  $59.8 \pm 17.8$  years without a significant difference between the centers.

In total, 39.8% of the patients required hospitalization, 12.1% were DH patients and 48.1% were ambulatory patients. Approximately 30.8% of the patients were urgently hospitalized, 21.2% of the cases had a planned admission, 22.2% needed a follow-up evaluation and 25.8% were at their first medical visit.

In Table 3 we report the age, gender, medical evaluation setting and disease category of patients according to their age category.

Gastrointestinal diseases were acute in 72.1% of the cases, chronic in 16.7% and neoplastic in 11.1%. In particular, chronic diseases were more frequent in younger participants (22.6% vs 9.0% in older patients,  $P < 0.001$ ), while neoplastic diseases were more represented in the elderly patients (5.6% in younger patients vs 18.8%,  $P < 0.001$ ).

Table 4 shows the prevalence of each pathology included in the three categories: Acute disease, chronic diseases and cancers according to age.

### Undernutrition

The mean prevalence of undernutrition in our population was 12.1%:4.6% in the ambulatory and DH settings and 19.6% in patients requiring hospitalization.

The undernourished patients were affected by chronic, acute and neoplastic disease at rates of 8%, 74% and 18%, respectively.

In Table 5 we report the distribution of undernutrition, risk of malnutrition, obesity and overweight among inpatients and outpatients in both categories of age. In both categories of age, the rate of undernourished inpatients was significantly higher compared to that of outpatients.

As shown in Figure 1, the prevalence of undernutrition in chronic, acute and neoplastic gastrointestinal diseases was 4.3%, 11.0% and 17.6%, respectively, with a prevalence significantly higher in neoplastic patients than in those with chronic disease ( $P = 0.03$ ). The linear trend test showed that the prevalence of undernutrition was significantly higher in hospital admitted patients ( $P = 0.01$ ).

The logistical regression analysis corrected for age, gender and acute, chronic and neoplastic disease showed that gastrointestinal cancer was a risk factor for undernutrition with an odds ratio of 2.7 (95%CI: 1.2-6.4,  $P = 0.02$ ).

### Risk of malnutrition

The mean prevalence of risk of malnutrition in our population was 23.8%. In Table 5 we show the prevalence of risk of malnutrition among inpatients and outpatients, and in Table 6 we report the prevalence of risk of malnutrition according to the three screening tests and age group. Of the < 65-year-old patients, the 24.7% of inpatients were at risk of malnutrition; in the elderly participants, the MNA screening tool revealed a risk of malnutrition in inpatients that was higher than that of elderly outpatients (69.2% vs 40.6%, respectively,  $P < 0.001$ ).



**Table 2** Characteristics of the patients in the 19 gastroenterological units participating in the study

Centers	n	M	F	Age (average ± DS)	Ambulatory	DH	Inpatients	MUST	NRS	MNA	Weight (kg)	Weight loss (%)	BMI
Bolzano	21	61.90%	38.10%	67.5 ± 17.2	0.00%	0.00%	100.00%	-	2.2 ± 1.5	16.8 ± 4.3	71.6 ± 16.4	-4.7 ± 6.2	24.8 ± 4.4
Fiemme del Cavalese	17	57.1%	42.9%	56.2 ± 25.1	57.1%	0.0%	42.9%	0.8 ± 1.3	1.7 ± 1.4	19.0 ± 9.9	66.9 ± 5.1	-2.5 ± 6.9	23.1 ± 2.4
Pordenone	14	25.0%	75.0%	48.7 ± 24.0	100.0%	0.0%	0.0%	1.0 ± 1.2	-	22.0 ± 0.0	58.3 ± 12.7	0.0 ± 0.0	21.3 ± 3.6
Udine	10	50.0%	50.0%	51.6 ± 8.7	70.0%	0.0%	30.0%	0.4 ± 0.7	-	13.0 ± 0.0	75.5 ± 16.0	-2.0 ± 5.7	25.9 ± 5.2
Como	12	72.2%	27.8%	65.3 ± 17.9	0.0	22.2%	77.8%	1.7 ± 2.1	2.3 ± 1.5	18.6 ± 5.4	73.5 ± 22.7	-7.6 ± 9.4	25.8 ± 6.7
Milano	17	64.0%	36.0%	64.9 ± 19.2	0.0	0.0%	100.0%	-	1.7 ± 1.4	9.5 ± 3.1	69.4 ± 15.7	-2.8 ± 7.4	25.2 ± 4.7
Torino	38	50.0%	50.0%	58.9 ± 16.1	0.0	55.3%	44.7%	1.6 ± 1.7	2.2 ± 2.2	15.8 ± 4.9	65.3 ± 16.6	-0.9 ± 9.1	23.9 ± 4.5
Alto Vicentino di Santorso	32	40.6%	59.4%	68.2 ± 12.7	97.3	0.0%	2.7%	0.2 ± 0.6	0.5 ± 0.7	15.4 ± 4.6	71.3 ± 12.8	-2.3 ± 4.9	25.0 ± 3.9
Bassano del Grappa	25	48.0%	52.0%	48.3 ± 17.9	60.0	0.0%	40.0%	0.5 ± 0.9	0.8 ± 1.4	17.6 ± 4.8	68.0 ± 14.5	0.1 ± 9.0	23.9 ± 4.3
Legnano	16	87.5%	12.5%	53.0 ± 16.1	0.0	0.0%	100.0%	-	1.1 ± 1.6	15.2 ± 4.6	66.1 ± 13.5	-4.2 ± 12.3	23.0 ± 2.7
Ravenna	66	41.5%	58.5%	57.4 ± 19.4	52.5	21.9	25.6%	0.8 ± 1.3	1.3 ± 1.4	19.6 ± 2.8	67.7 ± 17.4	-1.5 ± 7.2	24.3 ± 5.4
Ancona	33	39.4	60.6	58.9 ± 19	100.0	0.0	0.0	0.1 ± 0.3	-	13.5 ± 4.8	70.8 ± 13.5	0.5 ± 2.5	25.7 ± 4.8
Napoli	26	53.8	46.1	59.1 ± 15.8	7.7	30.8	61.5	0.5 ± 0.9	1.3 ± 1.2	12.2 ± 2.7	67.9 ± 14.9	-1.2 ± 3.8	24.7 ± 5.6
Foggia	33	39.4	60.6	57.7 ± 18.2	66.6	6.1	27.3	0.3 ± 0.9	0.4 ± 0.8	15.0 ± 3.3	76.5 ± 21.9	-1.5 ± 3.0	28.6 ± 7.6
Trani	53	58.5	41.5	55.5 ± 18.1	62.1	10.3	27.6	0.5 ± 0.9	0.7 ± 1.1	13.4 ± 3.2	71.6 ± 14.5	1.1 ± 5.5	27.1 ± 5.5
Cosenza	58	53.9	46.1	58.8 ± 18.4	38.1	15.9	46.0	1.3 ± 1.7	2.1 ± 1.1	15.3 ± 3.7	67.0 ± 15.9	-3.8 ± 7.9	24.5 ± 4.8
Palermo	15	64.7	35.3	64.2 ± 10.1	0.0	0.0	100.0	-	1.3 ± 0.6	13.0 ± 4.5	77.5 ± 21.3	-1.3 ± 1.6	27.6 ± 6.7
Marsala	17	41.2	58.8	70.4 ± 9.5	88.2	0.0	11.8	0.6 ± 0.8	2.6 ± 0.9	18.0 ± 5.4	72.2 ± 12.4	-2.2 ± 3.5	27.7 ± 3.7
Siracusa	10	60.0	40.0	67.9 ± 1.3	20.0	0.0	80.0	0.8 ± 1.2	2.6 ± 1.5	15.4 ± 4.6	61.8 ± 7.8	-1.6 ± 4.9	23.9 ± 2.6
Total	513	51.4	48.6	59.8 ± 17.8	48.1	12.1	39.8	0.7 ± 0.5	1.5 ± 0.8	15.8 ± 2.9	69.7 ± 16.0	-1.7 ± 6.9	25.3 ± 5.3

M: Male; F: Females; DH: Day Hospital; MUST: Malnutrition Universal Screening Tool; NRS: Nutritional Risk Screening; MNA: Mini Nutritional Assessment; BMI: Body Mass Index.

**Table 3** Clinical features of evaluated patients according to age group *n* (%)

	Total cohort ( <i>n</i> = 513)	< 65 yr ( <i>n</i> = 289)	≥ 65 yr ( <i>n</i> = 218)	<i>P</i> value
Age (yr) (Mean ± SD)	59.8 ± 17.8	47.4 ± 12.8	76.1 ± 6.9	< 0.001 <sup>1</sup>
Male gender,	260 (51.4)	138 (47.8)	122 (56.2)	0.06 <sup>2</sup>
Setting				< 0.001 <sup>2</sup>
Inpatient	204 (39.8)	93 (32.2)	110 (50.7)	
Outpatient	308 (60.2)	196 (67.8)	107 (49.3)	
Disease				< 0.001 <sup>2</sup>
Acute	414 (72.1)	232 (71.8)	177 (72.2)	
Chronic	96 (16.7)	73 (22.6)	22 (9.0)	
Neoplastic	64 (11.1)	18 (5.6)	46 (18.8)	

*P* value: <sup>1</sup>*P* < 0.05. <sup>2</sup>Wilcoxon rank-sum (Mann-Whitney) test; <sup>3</sup>χ<sup>2</sup> test. Significant standardized adjusted residual.

Of the outpatients at risk of malnutrition, acute and chronic gastrointestinal diseases had the same prevalence (50%); ten outpatients were affected by cancer, but none were at risk of malnutrition. In this population, only the 17.7% of patients with chronic gastrointestinal disease and 8.8% of those with acute gastrointestinal disease were at risk of malnutrition.

The inpatients at risk of malnutrition were affected by acute disease in 61.5% and by gastrointestinal cancer in 38.5% of the cases.

The elderly patients at risk of malnutrition presented chronic, acute and neoplastic disease in 5.2%, 67.0%, and 27.8% of the cases, respectively.

Figure 2 shows that the frequency of risk of malnutrition increased progressively with hospitalization, reaching statistical significance (*P* < 0.007) in the presence

of neoplasm.

### Overweight and obesity

The prevalence of overweight and obesity in our population was, respectively, 28.6% and 15.6%. In Table 5, we report the rate of overweight and obesity in outpatients (31.7% and 18.3%, respectively) and in inpatients (25.5% and 13.0%, respectively) according to age group. Moreover, the rate of overweight and obesity did not show a difference in age. The prevalence of overweight and obesity was, respectively, 28.7% and 19.1% in chronic, 29.1% and 15.7% in acute, and 26.4% and 11.3% in neoplastic disease.

In our population, we found that no obese outpatients presented a weight loss > 10% in the last 3-6 mo, while the prevalence of risk of malnutrition was 15% higher

**Table 4** Prevalence and number of patients with chronic disease, acute disease and cancer according to age group

Chronic disease	%	< 65 yr	≥ 65 yr	P value	Acute disease	%	< 65 yr	≥ 65 yr	P value	Cancer	%	< 65 yr	≥ 65 yr	P value
GERD	8.90	35	18	0.123	Dysphagia	2.7	7	9	0.199	Esophagus	0.7	0	4	0.033
Achalasia	0.20	1	0	0.577	Dyspepsia	9.3	25	30	0.046	Stomach	1.3	3	5	0.219
Chronic gastropathy	5.90	17	18	0.174	Epigastralgia	12.6	44	31	0.44	Small-large intestine	3	5	13	0.01
Chronic viral hepatitis	4.20	17	8	0.194	Other abdominalgia	17.7	53	52	0.78	Pancreas	0.5	1	2	0.394
Chronic alcoholic hepatitis	3.20	14	5	0.113	Acute diarrhea	2.5	8	6	0.602	Liver	3.4	7	13	0.036
NAFLD	4.50	13	14	0.206	Acute constipation	1.5	7	2	0.18	Biliary tree	2	3	9	0.024
Other chronic hepatitis	1.30	3	5	0.211	Digestive bleeding	5.6	13	20	0.027					
Compensated cirrhosis	14.70	49	38	0.441	Acute hepatitis	3.4	13	7	0.315					
Chronic pancreatitis	1.20	4	3	0.632	Cirrhosis complicated	11.5	39	29	0.478					
Non-IBD chronic diarrhea	3.50	11	10	0.391	Hematochezia	3.5	7	14	0.022					
Crohn's disease	6.60	33	6	0.0002	IBD exacerbation	6.1	33	3	0.000033					
Ulcerative colitis	4.5	24	3	0.00036	Acute pancreatitis	4.9	17	12	0.515					
Chronic constipation	5.2	13	18	0.053										
Celiac disease	1.7	10	0	0.004										

GERD: Gastric esophagitis reflux diseases; NAFLD: Non-alcoholic fatty liver disease; IBD: Inflammatory bowel disease.

**Table 5** Patients with nutritional abnormalities in the 19 gastroenterological centers participating in the study *n* (%)

	Outpatients		Inpatients		P value
	< 65 yr	> 65 yr	< 65 yr	> 65 yr	
Undernutrition	8 (4.2)	6 (5.7)	24 (23.9) <sup>1</sup>	15 (15.6) <sup>2</sup>	<sup>1</sup> P < 0.001 <sup>2</sup> P
Risk of Malnutrition	24 (12.2)	43 (40.6)	21 (24.7)	64 (69.2) <sup>3</sup>	<sup>3</sup> P
Obesity	34 (18.3)	19 (17.5)	15 (17.2)	10 (10.5)	NS
Overweight	52 (26.5)	46 (42.5)	18 (20.7)	27 (28.4)	NS

<sup>1</sup>P < 0.001 out- vs inpatient < 65; <sup>2</sup>P = 0.02 out- vs inpatient ≥ 65; <sup>3</sup>P < 0.001 out- vs inpatient > 65.

**Table 6** Prevalence of risk of malnutrition according to age group

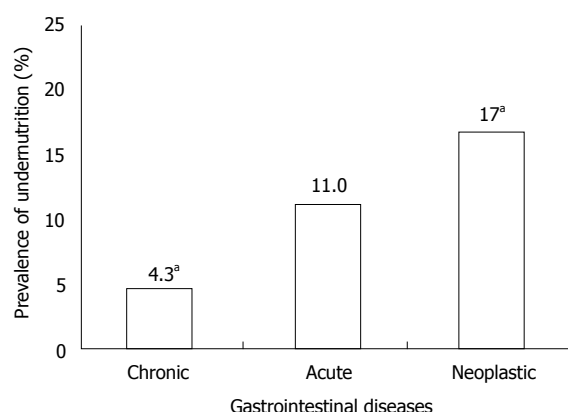
Nutritional risk test	Total cohort (n = 513)	< 65 yr (n = 289)	≥ 65 yr (n = 218)	P value
MUST				0.45
< 2 (%)	274 (89.0)	172 (87.8)	97 (90.7)	
≥ 2 (%)	34 (11.0)	24 (12.2)	10 (9.3)	
NRS 2002				0.002
< 3 (%)	112 (63.3)	61 (75.3)	51 (53.1)	
≥ 3 (%)	65 (36.7)	20 (24.7)	45 (46.9)	
MNA 17%-25%	115 (54.2)	-	115 (54.5)	

MUST: Malnutrition Universal Screening Tool; NRS: Nutritional Risk Screening; MNA: Mini Nutritional Assessment.

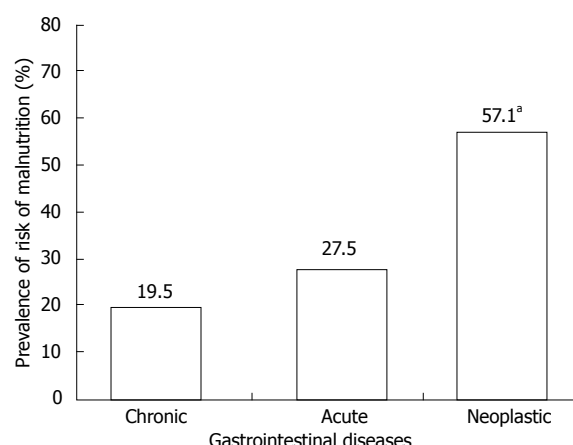
in elderly subjects (36.8%). The rate of undernutrition was 12% in the hospitalized obese patients, and the prevalence of risk of malnutrition was 13.3% in young obese inpatients and increased up to 80% in those > 65

years old.

Of the overweight outpatients, the rate of undernutrition was 2%, while it was 8.9% in overweight inpatients. The rate of overweight outpatients at risk of malnutrition was



**Figure 1** Prevalence of undernutrition in presentations of acute, chronic and neoplastic gastrointestinal diseases. <sup>a</sup> $P = 0.03$ , neoplastic vs chronic. Linear trend test:  $P = 0.01$ .



**Figure 2** Prevalence of risk of malnutrition in presentations of acute, chronic and neoplastic gastrointestinal diseases. <sup>a</sup> $P < 0.007$ , neoplastic vs chronic and acute.

28.3%, but this rate reached 33.3% in those hospitalized.

## DISCUSSION

This study was designed to define the nutritional state of patients with gastroenterological disease. Regarding the diseases included in this study, we want to specify that cirrhotic patients were excluded because of the obscuring effect of compartmentalized ascites on body weight<sup>[31,36,49]</sup>. However, diseases causing reduced albumin levels, which decreases oncotic pressure and allows for diffuse fluid leakage into the interstitial space, were not excluded, as fluid retention has to be considered a direct consequence of malnutrition.

Our data found that undernutrition affected approximately 12% of all patients; in particular, we documented that the rate of prevalence of undernutrition was significantly higher in inpatients (20%) than in outpatients. This is a consequence of the fact that acute diseases requiring hospitalization reduce caloric intake because of the presence of abdominal pain, diarrhea and vomiting. The use of tools to evaluate the risk of malnutrition should allow us to focus our attention on patients who have not yet begun to lose weight.

It was also interesting to note that younger and neoplastic inpatients were more frequently malnourished than the other groups, and this was due to the high rate of chronic inflammatory gastrointestinal diseases in our younger population (IBD: 11.4% vs 1.4% and celiac disease: 3.5% vs 0% in < 65-year-old and > 65-year-old patients, respectively) and the metabolic abnormalities characterizing cancer cachexia. Indeed, logistic regression confirmed that (1) the rate of undernutrition increased with the severity of disease; and (2) gastrointestinal cancer was a risk factor for undernutrition.

Very little data can be found in the literature concerning the prevalence rates of undernutrition in gastroenterology units. In our population, the prevalence of undernutrition was similar to those reported in other European<sup>[8]</sup> and Italian studies<sup>[28]</sup> but differed from other studies<sup>[9,29,30,50]</sup> because of both (1) the different

tools used to evaluate malnutrition; and (2) the diverse stages of disease. In this study, we reported for the first time (1) the rate of undernutrition in gastroenterology outpatients; and (2) the correlation of undernutrition with hospital admission.

Regarding the risk of malnutrition, we want to emphasize that all of the screening tools we used were well-validated in identifying the patients who would develop undernutrition in the absence of an adequate nutritional care plan and that the NRS-2002 has shown a good predictive value for mortality, length of stay and complications. Few data have been published about the risk of malnutrition in the gastroenterology population<sup>[9,10,50]</sup>. In this study, we demonstrated that, in the gastroenterology department, inpatient and elderly patients had a greater frequency of risk of malnutrition than outpatients and younger patients, especially if affected by cancer; additionally, this risk was lower for those with chronic gastrointestinal disease. We must also highlight the fact that the NRS-2002 in inpatients was more frequently influenced by a reduction in caloric intake than by weight loss.

In our population, the NRS-2002 disclosed a risk of malnutrition in 36.7% of the inpatients. This value was lower than that reported in a Danish study evaluating gastro-surgery patients<sup>[9]</sup> but higher than data from Romanian gastroenterology departments<sup>[50]</sup>.

Moreover, while young inpatients were undernourished or at risk of malnutrition at a similar prevalence, elderly inpatients were at a greater risk of malnutrition. These data indicate that the management of malnutrition in gastrointestinal departments should have different targets according to patients' age: We should probably treat undernutrition with artificial nutrition in younger patients, while oral supplementation should be recommended to prevent malnutrition in elderly patients. Very limited data are available on the evaluation of the risk of malnutrition in outpatients. In this setting, our data indicated that patients with nutritional risk were more often affected by chronic disease, in which the catabolic

effects of inflammatory cytokines influence nutritional status<sup>[4,51,52]</sup>.

Overweight and obesity represent another aspect of malnutrition that entails excessive fat mass in body composition. In recent years, a number of works have reported an increasing incidence of obesity in the general population, but data on the prevalence of obesity and overweight in the gastroenterological population have been limited. The average prevalence of overweight-obesity in our study was 22.7%; this rate of obesity was lower than those reported in a hospital setting in previous Italian<sup>[28-30]</sup> reports but was higher than the Italian general population rate, especially in outpatients.

We also found that approximately 10% of the obese and overweight hospitalized patients were undernourished and that the risk of malnutrition was present in more than one-third of the obese and overweight gastroenterological patients, with rates that reached 80% in > 65-year-old obese inpatients.

The prevalence of obesity and overweight in outpatients was higher than in inpatients but was not statistically significant.

It is not surprising that in obese patients, undernutrition and risk of malnutrition could be present at the same time. An involuntary weight loss > 10% and/or reduction in caloric intake allowed us to identify patients who, despite having excess weight, met the criteria for malnutrition or risk of malnutrition. These data indicate that we must keep in mind that even obese patients can be malnourished and that we must investigate the risk of malnutrition especially among elderly gastroenterological patients, regardless of their weight at admission.

A possible bias of this study was the voluntary participation of the gastrointestinal units including centers that paid major attention to nutritional aspects. Another limitation of this work was the difference in the population size and in the frequency of disease, which was often determined by each center's particular experience; it was thus difficult to study undernutrition and the risk of malnutrition for each single disease.

Overall, our data noted that 55% of inpatients and 22% of outpatients were undernourished and at risk of malnutrition and that half of the outpatients and nearly one-third of inpatients were obese or overweight. In our population, only 19.7% and 36.6% of inpatients and outpatients, respectively, did not present nutritional abnormalities (weight loss, risk of malnutrition, overweight or obesity). These data indicate that 80.3% of inpatients and 63.4% of outpatients would require nutritional competence in gastrointestinal units to assess the degree of malnutrition, to correctly design appropriate therapeutic programs to improve protein-caloric alterations and to prevent complications.

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## COMMENTS

### Background

Malnutrition has adverse effects on clinical outcomes, but many health care workers do not adequately consider it as a relevant aspect of the clinical management of patients. In the literature, few data are available regarding the prevalence of malnutrition (undernutrition, obesity,) and risk of malnutrition in European and Italian gastroenterology departments, with rates that depend on the criteria adopted for their identification, the medical or surgical setting and the age of the patients.

### Research frontiers

A better understanding of the prevalence of malnutrition and nutritional risk according to the severity of disease (chronic, acute and cancer) in outpatients and inpatients would facilitate the identification of patients with impairment of nutritional status and with adequate nutritional management.

### Innovations and breakthroughs

For the first time, they studied undernutrition, risk of malnutrition (using three different nutritional screening tools) and obesity according to the severity of gastroenterological disease (chronic, acute and cancer) in both admitted patients and outpatients.

### Applications

The authors' data showed that there was a different distribution of undernutrition, risk of malnutrition and obesity according to the severity of disease and age group among inpatients and outpatients, which indicates that an appropriate nutritional care plan in gastrointestinal departments to achieve different nutritional targets may be needed.

### Terminology

Undernutrition: When patients presented an unintentional (*i.e.*, without voluntary dietary restriction) weight loss > 10% in the last 3-6 mo; The MUST (Malnutrition Universal Screening Tool), NRS-2002 (Nutritional Risk Screening Score 2002) and MNA (Mini Nutritional Assessment) are three screening nutritional tests that identify patients at risk of malnutrition; BMI: Body mass index (calculated by dividing the weight in kg by the square of height in meters). Obesity: BMI  $\geq$  30; overweight: BMI between 25 and 29.9.

### Peer-review

The authors have excluded cirrhotics because of the obscuring effect of ascitis and or edema. Inflammatory diseases may cause a drop in serum albumin



levels that decrease oncotic pressure and favors fluid leakage to the interstitial space, that may reach up to 5 l before edema is clinically evident.

## REFERENCES

- Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM, de van der Schueren MA, Singer P. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. *Clin Nutr* 2015; **34**: 335-340 [PMID: 25799486 DOI: 10.1016/j.clnu.2015.03.001]
- Lancha A, Frühbeck G, Gómez-Ambrosi J. Peripheral signalling involved in energy homeostasis control. *Nutr Res Rev* 2012; **25**: 223-248 [PMID: 23174510 DOI: 10.1017/S0954422412000145]
- Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. *Endocr Regul* 2009; **43**: 157-168 [PMID: 19908934]
- Roubenoff R. Molecular basis of inflammation: relationships between catabolic cytokines, hormones, energy balance, and muscle. *JPEN J Parenter Enteral Nutr* 2008; **32**: 630-632 [PMID: 18974242 DOI: 10.1177/0148607108324875]
- Amitani M, Asakawa A, Amitani H, Inui A. Control of food intake and muscle wasting in cachexia. *Int J Biochem Cell Biol* 2013; **45**: 2179-2185 [PMID: 23911307 DOI: 10.1016/j.biocel.2013.07.016]
- McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital. *BMJ* 1994; **308**: 945-948 [PMID: 8173401 DOI: 10.1136/bmj.308.6934.945]
- Imoberdorf R, Meier R, Krebs P, Hangartner PJ, Hess B, Stäubli M, Wegmann D, Rühl M, Ballmer PE. Prevalence of undernutrition on admission to Swiss hospitals. *Clin Nutr* 2010; **29**: 38-41 [PMID: 19573958 DOI: 10.1016/j.clnu.2009.06.005]
- Edington J, Boorman J, Durrant ER, Perkins A, Giffin CV, James R, Thomson JM, Oldroyd JC, Smith JC, Torrance AD, Blackshaw V, Green S, Hill CJ, Berry C, McKenzie C, Vicca N, Ward JE, Coles SJ. Prevalence of malnutrition on admission to four hospitals in England. The Malnutrition Prevalence Group. *Clin Nutr* 2000; **19**: 191-195 [PMID: 10895110 DOI: 10.1054/clnu.1999.0121]
- Rasmussen HH, Kondrup J, Staun M, Ladefoged K, Kristensen H, Wengler A. Prevalence of patients at nutritional risk in Danish hospitals. *Clin Nutr* 2004; **23**: 1009-1015 [PMID: 15380890 DOI: 10.1016/j.clnu.2004.01.001]
- Pirlich M, Schütz T, Norman K, Gastell S, Lübke HJ, Bischoff SC, Bolder U, Frieling T, Gülden-zoph H, Hahn K, Jauch KW, Schindler K, Stein J, Volkert D, Weimann A, Werner H, Wolf C, Zürcher G, Bauer P, Lochs H. The German hospital malnutrition study. *Clin Nutr* 2006; **25**: 563-572 [PMID: 16698132 DOI: 10.1016/j.clnu.2006.03.005]
- Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nutr* 2008; **27**: 5-15 [PMID: 18061312 DOI: 10.1016/j.clnu.2007.10.007]
- Kyle UG, Pirlich M, Schuetz T, Lochs H, Pichard C. Is nutritional depletion by Nutritional Risk Index associated with increased length of hospital stay? A population-based study. *JPEN J Parenter Enteral Nutr* 2004; **28**: 99-104 [PMID: 15080604 DOI: 10.1177/014860710402800299]
- Caccialanza R, Klersy C, Cereda E, Cameletti B, Bonoldi A, Bonardi C, Marinelli M, Dionigi P. Nutritional parameters associated with prolonged hospital stay among ambulatory adult patients. *CMAJ* 2010; **182**: 1843-1849 [PMID: 20940233 DOI: 10.1503/cmaj.091977]
- Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr* 2003; **22**: 235-239 [PMID: 12765661 DOI: 10.1016/S0261-5614(02)00215-7]
- Takahashi PY, Sauver JL, Olson TC, Huber JM, Cha SS, Ebbert JO. Association between underweight and hospitalization, emergency room visits, and mortality among patients in community medical homes. *Risk Manag Healthc Policy* 2013; **6**: 1-6 [PMID: 23378790 DOI: 10.2147/RMHP.S39976]
- Pérez de la Cruz A, Lobo Támer G, Orduña Espinosa R, Mellado Pastor C, Aguayo de Hoyos E, Ruiz López MD. [Malnutrition in hospitalized patients: prevalence and economic impact]. *Med Clin (Barc)* 2004; **123**: 201-206 [PMID: 15282072 DOI: 10.1016/S0025-7753(04)74461-9]
- Beck AM, Balknäs UN, Fürst P, Hasunen K, Jones L, Keller U, Melchior JC, Mikkelsen BE, Schauder P, Sivonen L, Zinck O, Øien H, Ovesen L. Food and nutritional care in hospitals: how to prevent undernutrition--report and guidelines from the Council of Europe. *Clin Nutr* 2001; **20**: 455-460 [PMID: 11534942 DOI: 10.1054/clnu.2001.0494]
- Kyle UG, Kossovsky MP, Karsgaard VL, Pichard C. Comparison of tools for nutritional assessment and screening at hospital admission: a population study. *Clin Nutr* 2006; **25**: 409-417 [PMID: 16356595 DOI: 10.1016/j.clnu.2005.11.001]
- Mowe M, Bosaeus I, Rasmussen HH, Kondrup J, Unosson M, Rothenberg E, Irtun Ø. Insufficient nutritional knowledge among health care workers? *Clin Nutr* 2008; **27**: 196-202 [PMID: 18295936 DOI: 10.1016/j.clnu.2007.10.014]
- Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr* 2003; **22**: 415-421 [PMID: 12880610 DOI: 10.1016/S0261-5614(03)00098-0]
- Sorensen J, Kondrup J, Prokopowicz J, Schiesser M, Krähenbühl L, Meier R, Liberda M. EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. *Clin Nutr* 2008; **27**: 340-349 [PMID: 18504063 DOI: 10.1016/j.clnu.2008.03.012]
- Velasco C, García E, Rodríguez V, Frias L, Garriga R, Alvarez J, García-Peris P, León M. Comparison of four nutritional screening tools to detect nutritional risk in hospitalized patients: a multicentre study. *Eur J Clin Nutr* 2011; **65**: 269-274 [PMID: 21081958 DOI: 10.1038/ejcn.2010.243]
- Ambrose T, Cullen S, Baker G, Smith M, Elia M, Leach R, De Silva A. Obesity: a window of opportunity to intervene? Characteristics and management of morbidly obese adult inpatients in three trusts in Southern England. *Clin Med (Lond)* 2013; **13**: 472-476 [PMID: 24115704 DOI: 10.7861/clinmedicine.13-5-472]
- Migliore E, Pagano E, Mirabelli D, Baldi I, Gregori D, Zocchetti C, Tuzzi C, Balzola F, Petroni ML, Merletti F. Hospitalization rates and cost in severe or complicated obesity: an Italian cohort study. *BMC Public Health* 2013; **13**: 544 [PMID: 23738687 DOI: 10.1186/1471-2458-13-544]
- Luchsinger JA, Lee WN, Carrasquillo O, Rabinowitz D, Shea S. Body mass index and hospitalization in the elderly. *J Am Geriatr Soc* 2003; **51**: 1615-1620 [PMID: 14687392 DOI: 10.1046/j.1532-5415.2003.51513.x]
- Han E, Truesdale KP, Taber DR, Cai J, Juhaeri J, Stevens J. Impact of overweight and obesity on hospitalization: race and gender differences. *Int J Obes (Lond)* 2009; **33**: 249-256 [PMID: 19153585 DOI: 10.1038/ijo.2008.193]
- Ringbäck Weitoft G, Eliasson M, Rosén M. Underweight, overweight and obesity as risk factors for mortality and hospitalization. *Scand J Public Health* 2008; **36**: 169-176 [PMID: 18519281 DOI: 10.1177/1403494807085080]
- Comi D, Palmo A, Brugnani M, D'Amicis A, Costa A, D'Andrea F, Del Toma E, Domeniconi D, Fusco MA, Gatti E, Lesi C, Lucchin L. The hospital malnutrition Italian study. *Clin Nutr* 1998; **17** (Suppl 1): 52 [DOI: 10.1016/S0261-5614(98)80239-2]
- Lucchin L, D'Amicis A, Gentile MG, Battistini NC, Fusco MA, Palmo A, Muscaritoli M, Contaldo F, Cereda E, the PIMAI group. An Italian investigation on nutritional risk at hospital admission: The PIMAI (Project: Iatrogenic MAlnutrition in Italy) study. *Clin Nutr Metabol* 2009; **4**: 199-202 [DOI: 10.1016/j.clnm.2009.05.012]
- Cereda E, Pedrolli C, Lucchin L, D'Amicis A, Gentile MG, Battistini NC, Fusco MA, Palmo A, Muscaritoli M. Fluid intake and nutritional risk in non-critically ill patients at hospital referral. *Br J Nutr* 2010; **104**: 878-885 [PMID: 20447327 DOI: 10.1017/S0007114510001492]
- Guglielmi FW, Mastronuzzi T, Laddaga L, De Marco M, Scatigna F, Panella C, Francavilla A. Clinical utility of the bioelectrical impedance for evaluation body composition in patients with gastroenterological disease. *Ital J Gastroenterol* 1990; **22**: 250
- Guglielmi FW, Mastronuzzi T, De Marco M, Laddaga L, Scatigna F, Panella C, Francavilla A. Calorimetric data of cirrhotic patients with



- and without hepatocellular carcinoma: role of malnutrition. *Ital J Gastroenterol* 1991; **23**: 308-309
- 33 **Guglielmi FW**, Panella C, Buda A, Budillon G, Caregaro L, Clerici C, Conte D, Federico A, Gasbarrini G, Guglielmi A, Loguercio C, Losco A, Martines D, Mazzuoli S, Merli M, Mingrone G, Morelli A, Nardone G, Zoli G, Francavilla A. Nutritional state and energy balance in cirrhotic patients with or without hypermetabolism. Multicentre prospective study by the 'Nutritional Problems in Gastroenterology' Section of the Italian Society of Gastroenterology (SIGE). *Dig Liver Dis* 2005; **37**: 681-688 [PMID: 15978878 DOI: 10.1016/j.dld.2005.03.010]
  - 34 **Loguercio C**, Sava E, Marmo R, del Vecchio Blanco C, Coltorti M. Malnutrition in cirrhotic patients: anthropometric measurements as a method of assessing nutritional status. *Br J Clin Pract* 1990; **44**: 98-101 [PMID: 2344428]
  - 35 **Madden AM**, Morgan MY. A comparison of skinfold anthropometry and bioelectrical impedance analysis for measuring percentage body fat in patients with cirrhosis. *J Hepatol* 1994; **21**: 878-883 [PMID: 7890906 DOI: 10.1016/S0168-8278(94)80253-X]
  - 36 **Morgan MY**, Madden AM, Soulsby CT, Morris RW. Derivation and Validation of a New Global Method for Assessing Nutritional Status in Patients with Cirrhosis. *Hepatology* 2006; **44**: 823-835 [PMID: 17006918 DOI 10.1002/hep.21358]
  - 37 **Capristo E**, Addolorato G, Mingrone G, Greco AV, Gasbarrini G. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. *Am J Gastroenterol* 1998; **93**: 2411-2419 [PMID: 9860401 DOI: 10.1111/j.1572-0241.1998.00696.x]
  - 38 **Guglielmi FW**, Rizzi M, Mazzuoli S, Regano N, Leogrande G, Addante A, Guglielmi A, Panella C, Francavilla A, Di Leo A. Negative energy balance in Crohn's disease causes malnutrition and impaired muscle function. *Dig Liver Dis* 2009; **41S**: S131 [DOI 10.1016/S1590-8658(09)60344-3]
  - 39 **Mazzuoli S**, Addante I, Regano N, Rizzi M, Fregnan S, Leogrande G, Guglielmi A, Guglielmi FW. Prevalence of malnutrition in patients with moderate-severe Crohn's disease: the role of NRS2002. *Nutritional Therapy and Metabolism SINPE News* 2011; **4**: 9
  - 40 **Hussain Z**, Quigley EM. Gastrointestinal issues in the assessment and management of the obese patient. *Gastroenterol Hepatol* (N Y) 2007; **3**: 559-569 [PMID: 21960865]
  - 41 **Hurt RT**, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: challenges, health initiatives, and implications for gastroenterologists. *Gastroenterol Hepatol* (NY) 2010; **6**: 780-792 [PMID: 21301632]
  - 42 **Kirovski G**, Schacherer D, Wobser H, Huber H, Niessen C, Beer C, Schölmerich J, Hellerbrand C. Prevalence of ultrasound-diagnosed non-alcoholic fatty liver disease in a hospital cohort and its association with anthropometric, biochemical and sonographic characteristics. *Int J Clin Exp Med* 2010; **3**: 202-210 [PMID: 20827318 DOI: 10.1055/s-0029-1246560]
  - 43 **Vellinga A**, O'Donovan D, De La Harpe D. Length of stay and associated costs of obesity related hospital admissions in Ireland. *BMC Health Serv Res* 2008; **8**: 88 [PMID: 18426608 DOI: 10.1186/1472-6963-8-88]
  - 44 **Stratton RJ**, Hackston A, Longmore D, Dixon R, Price S, Stroud M, King C, Elia M. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *Br J Nutr* 2004; **92**: 799-808 [PMID: 15533269 DOI: 10.1079/BJN20041258]
  - 45 **Kondrup J**, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 2003; **22**: 321-336 [PMID: 12765673 DOI: 10.1016/S0261-5614(02)00214-5]
  - 46 **Guigoz Y**, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev* 1996; **54**: S59-S65 [PMID: 8919685 DOI: 10.1111/j.1753-4887.1996.tb03793.x]
  - 47 **Vellas B**, Guigoz Y, Garry PJ, Nourhashemi F, Bannahum D, Lauque S, Albaredo JL. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 1999; **15**: 116-122 [PMID: 9990575 DOI: 10.1016/S0899-9007(98)00171-3]
  - 48 **Guigoz Y**, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. *Clin Geriatr Med* 2002; **18**: 737-757 [PMID: 12608501 DOI: 10.1016/S0749-0690(02)00059-9]
  - 49 **Fernandes SA**, Bassani L, Nunes FF, Aydos ME, Alves AV, Marroni CA. Nutritional assessment in patients with cirrhosis. *Arg Gastroenterol* 2012; **49**: 19-27 [PMID: 22481682]
  - 50 **Gheorghe C**, Pascu O, Iacob R, Goldis A, Tantau M, Dumitru E, Dobru D, Miutescu E, Saftoiu A, Fraticiu A, Tomescu D, Gheorghe L. Nutritional Risk Screening and Prevalence of Malnutrition on Admission to Gastroenterology Departments: A Multicentric Study. *Chirurgia* (Bucur) 2013; **108**: 535-41
  - 51 **Catapano G**, Pedone C, Nunziata E, Zizzo A, Passantino A, Incalzi RA. Nutrient intake and serum cytokine pattern in elderly people with heart failure. *Eur J Heart Fail* 2008; **10**: 428-434 [PMID: 18353717 DOI: 10.1016/j.ejheart.2008.02.016]
  - 52 **Yang YM**, Sun TY, Liu XM. The role of serum leptin and tumor necrosis factor-alpha in malnutrition of male chronic obstructive pulmonary disease patients. *Chin Med J* (Engl) 2006; **119**: 628-633 [PMID: 16635406]

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## Systematic review of laparoscopic vs open surgery for colorectal cancer in elderly patients

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### Abstract

**AIM:** To verify the safety and validity of laparoscopic surgery for the treatment of colorectal cancer in elderly patients.

**METHODS:** A meta-analysis was performed of a systematic search of studies on an electronic database. Studies that compared laparoscopic colectomy (LAC) in elderly colorectal cancer patients with open colectomy (OC) were retrieved, and their short and long-term outcomes compared. Elderly people were defined as 65 years old or more. Inclusion criteria were set at: Resection of colorectal cancer, comparison between laparoscopic and OC and no significant difference in backgrounds between groups.

**RESULTS:** Fifteen studies were identified for analysis. LAC was performed on 1436 patients, and OC performed on 1810 patients. In analyses of short-term outcomes, operation time for LAC was longer than for OC (mean difference = 34.4162, 95%CI: 17.8473-50.9851,  $P < 0.0001$ ). The following clinical parameters were lower in LAC than in OC: Amount of estimated blood loss (mean difference = -93.3738, 95%CI: -132.3437 to -54.4039,  $P < 0.0001$ ), overall morbidity (OR = 0.5427, 95%CI: 0.4425-0.6655,  $P < 0.0001$ ), incisional surgical site infection (OR = 0.6262, 95%CI: 0.4310-0.9097,  $P = 0.0140$ ), bowel obstruction and ileus (OR = 0.6248, 95%CI: 0.4519-0.8638,  $P = 0.0044$ ) and cardiovascular complications (OR = 0.4767, 95%CI: 0.2805-0.8101,  $P = 0.0062$ ). In analyses of long-term outcomes (median follow-up period: 36.4 mo in LAC, 34.3 mo in OC), there was no significant difference in overall survival (mean difference = 0.8321, 95%CI: 0.5331-1.2990,  $P = 0.4187$ ) and disease specific survival (mean difference = 1.0254, 95%CI: 0.6707-1.5675,  $P = 0.9209$ ). There was also no significant difference in the number of dissected lymph nodes (mean difference = -0.1360, 95%CI: -4.0553-3.7833,  $P = 0.9458$ ).

**CONCLUSION:** LAC in elderly colorectal cancer patients had benefits in short-term outcomes compared with OC except operation time. The long-term outcomes and oncological clearance of LAC were similar to that of OC. These results support the assertion that LAC is an effective procedure for elderly patients with colorectal cancer.

**Key words:** Laparoscopic surgery; Systematic review; Meta-analysis; Colorectal cancer; Elderly patient

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**Core tip:** Safety and effectiveness of laparoscopic surgery (LAC) in elderly has been unknown. A meta-analysis was performed of a systematic search of studies on an electronic database. Studies that compared LAC in elderly colorectal cancer patients with open colectomy (OC) were retrieved, and their short and long-term outcomes compared. Fifteen studies which had 1436 LAC and 1810 OC were identified. In short-term outcomes, blood loss, morbidity, incisional surgical site infection, bowel obstruction and cardiovascular complications were superior in LAC except operation time. There was no significant difference in long-term outcomes. LAC is an effective procedure for elderly with colorectal cancer.

Fujii S, Tsukamoto M, Fukushima Y, Shimada R, Okamoto K, Tsuchiya T, Nozawa K, Matsuda K, Hashiguchi Y. Systematic review of laparoscopic vs open surgery for colorectal cancer in elderly patients. *World J Gastrointest Oncol* 2016; 8(7): 573-582 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v8/i7/573.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v8.i7.573>

## INTRODUCTION

People are living longer across the globe. According to the World Health Organization, 6.9% of the world was over the age of 65 in 2000 with an estimated increase to 10.4% in 2025 and a further rise to 16.4% in 2050<sup>[1]</sup>. This estimation is valid in all regions of the world. Average life expectancies in 2025 are estimated to be 77 years old in the Americas and Europe and 72 years old in Asia. Colorectal cancer is the third most common malignant neoplasm in the world and aging is assumed to be one of the risk factors for colorectal carcinogenesis<sup>[2]</sup>. Elderly patients have a higher American Society of Anesthesiologists score, higher cardiac and pulmonary comorbidity rate and lower preoperative nutritional conditioning than younger patients<sup>[3-5]</sup>. Therefore, there is a high risk associated with even minimally invasive surgery in elderly patients. Several studies have reported the benefits of laparoscopic colorectal surgery in elderly patients<sup>[6-10]</sup>. Most studies concluded that laparoscopic surgery had a lower postoperative morbidity rate and shorter length of hospital stay when compared to open surgery. Several large-scale systematic reviews that

compare laparoscopic colorectal surgery with open surgery have been published in recent years<sup>[11,12]</sup>. They report that laparoscopic surgery has lower mortality, lower overall morbidity, lower cardiac and respiratory complications, lower wound infection and shorter length of hospital stay. However, they analyzed both colorectal cancer and benign diseases together. The surgical procedure for colorectal cancer differs from that for benign disease because optimal lymph node dissection and resection, with a securing safety margin, are vital in malignant neoplasm surgery. Therefore, a study analyzing laparoscopic surgery that targeted only colorectal cancer was required.

Moreover, the results of previous reviews reported only short-term outcomes. The evaluation of long-term outcomes is very important in the analysis of treatment efficacy for malignant neoplasia. The purpose of the present review is to clarify the benefits of laparoscopic surgery in elderly patients with colorectal cancer. We analyzed not only short-term but also long-term outcomes.

## MATERIALS AND METHODS

### Eligibility criteria

Elderly people were defined as 65 years old or more, as outlined by the World Health Organization<sup>[1]</sup>. All studies were limited to randomized controlled or comparative studies. The subject of each study was limited to colorectal cancer and studies that included any benign disease were excluded. Backgrounds were similar between both groups, and had at least 15 patients in one group. The results had to include a comparison between laparoscopic and open surgery.

### Outcomes

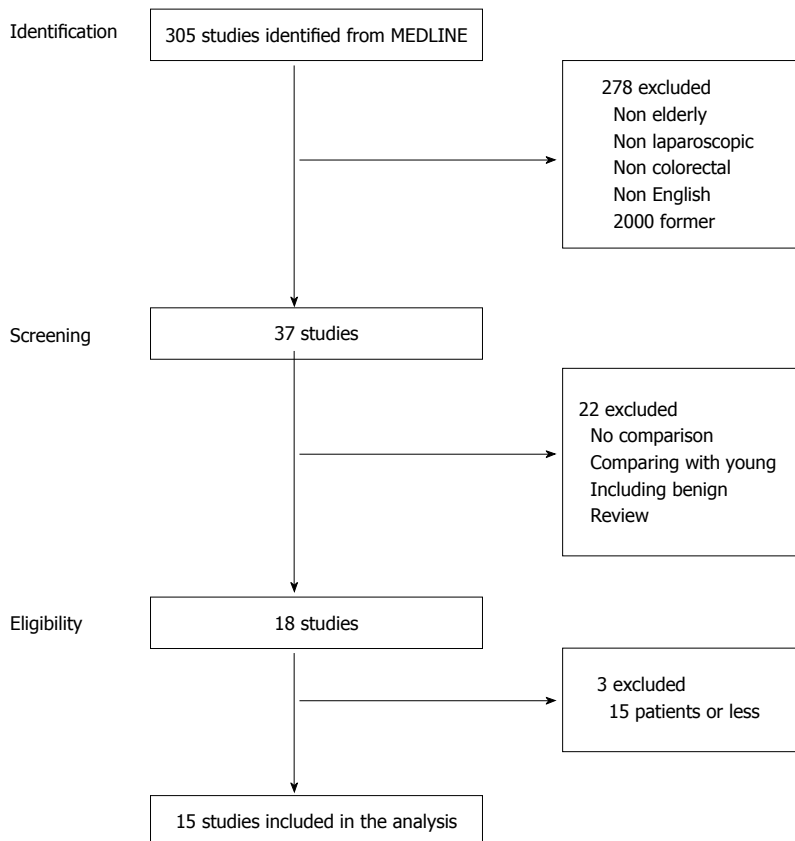
Short-term outcomes analyzed in the present study were as follows: Operative time, amount of estimated blood loss, mortality, overall morbidity, incisional surgical site infection, deep surgical site infection, anastomotic leakage, bowel obstruction and ileus, pneumonia, cardiovascular complication, time of normal bowel function and length of postoperative hospital stay. Duration of short-term was defined after the operation within 30 d.

The overall and disease specific survival rates were measured as long-term outcomes.

The number of dissected lymph nodes was used as an indicator of oncological clearance.

### Study selection

The literature search was performed electronically using PubMed (MEDLINE). The search terms were as follows: Elderly or old, colorectal cancer or colon cancer, and laparoscopic surgery or laparoscopic colectomy (LAC) in combination with Boolean operators AND or OR. The language was limited to English. Studies were selected from those published after 2000 because they included the long-term results of several randomized



controlled studies that compared laparoscopic and open surgery<sup>[13-18]</sup>. Moreover, developments in laparoscopic surgery instrumentation might influence short-term results in studies conducted in more recent years.

### Assessment of study quality

The number of randomized controlled study was only one in this meta-analysis<sup>[19]</sup>. The randomized controlled study was assessed for methodological quality using the Cochrane Handbook<sup>[20]</sup>. Five of six items were at low risk of bias. Blinding of the study was not possible.

The comparative studies were assessed by the Newcastle-Ottawa Quality Assessment Scale (NOS)<sup>[21]</sup>. Twelve of 14 studies had 6 or more star points on the NOS scale.

### Statistical analysis

The odds ratios (ORs) for each study and 95% CIs were calculated from event numbers of categorical variables of short-term results. Pooled ORs were calculated using a random effect model. The mean value difference between continuous variables of short-term results and the number of dissected lymph nodes was also calculated using a random effect model. In the analysis of long-term results, 95% CIs of survival comparison and the number of patients in each study were synthesized using a random effect model. Synthesis of data was performed using the DerSimonian-Laird method<sup>[22]</sup>. Study heterogeneity was checked by means of Cochran's *Q* statistic. If the *P* value of the heterogeneity test was

less than 0.05 in significance level, a null hypothesis of homogeneity was dismissed and study heterogeneity was proved. Publication bias among the studies was checked using the Egger test or Begg test accordingly. If the *P* value for publication bias was less than 0.10 a null hypothesis of no bias was dismissed and publication bias was confirmed.

## RESULTS

### Study profile

Thirty seven studies were identified by the first screening of MEDLINE. The reviews and studies that included benign disease cases or no data comparison between laparoscopic and open surgery were excluded. Finally, 15 studies were selected for analysis (Figure 1)<sup>[19,23-36]</sup>. The types of studies were as follows: 1 randomized controlled, 2 case-matched, 1 prospective comparative and 11 retrospective comparative studies. In total, 1436 laparoscopic surgeries and 1810 open surgeries were analyzed. Conversion to open surgery was described in 9 studies. The range of conversion rate was between 0% and 13.9%, and the incidence of total patients was 4.5%. A summary of study characteristics is shown in Table 1.

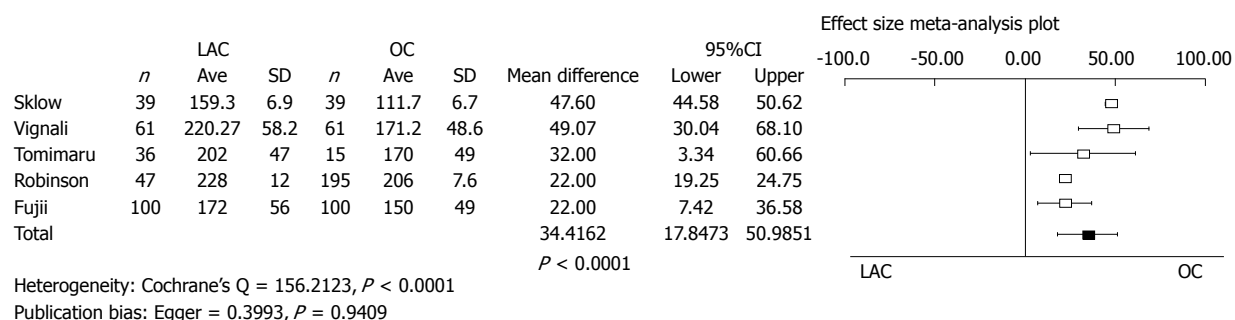
### Short-term outcomes

**Operation time:** Five studies reported operative time as the mean value with standard deviation. The operation time of LAC was significantly longer than OC (mean difference = 34.4162, 95%CI: 17.8473-50.9851, *P* <

**Table 1** Characteristics of studies

Ref.	Year	Study type	Age	Age		Patient	No. of LAC	No. of OC	Convert (%)	ASA (1-2/3-4)		Gender (M/F)		NOS
				LAC	OC					LAC	OC	LAC	OC	
Sklow <i>et al</i> <sup>[23]</sup>	2003	Case-matched	76	81.4 ± 0.83	81.8 ± 0.91	All cancer	39	39		19/20	10/29	22/17	21/18	6
Vignali <i>et al</i> <sup>[24]</sup>	2005	Case-matched	80	82.3 ± 2.3	83.1 ± 3.1	All cancer	61	61	4 (6.6)	2.5 ± 0.1	2.6 ± 0.6	29/32	29/32	6
Feng <i>et al</i> <sup>[25]</sup>	2006	Retro, comparative	71	77.8 ± 5.1	76.9 ± 6.1	All cancer	51	102	2 (3.9)					5
Tei <i>et al</i> <sup>[26]</sup>	2009	Retro, comparative	71	75.5 (71-89)	76.0 (71-93)	All cancer	51	78	3 (5.9)	Apr-37	63/15	32/19	43/35	6
Akiyoshi <i>et al</i> <sup>[27]</sup>	2009	Retro, comparative	75	79 (75-90)	79 (75-86)	Rectal cancer	44	43	0 (0)	Jun-38	Jul-36	21/23	23/20	3
Tomimaru <i>et al</i> <sup>[28]</sup>	2011	Retro, comparative	76	82.0 ± 4.6	81.9 ± 5.7	Colon cancer	36	15	5 (13.9)	20/16	8/7	13/23	7/8	8
Robinson <i>et al</i> <sup>[29]</sup>	2011	Retro, comparative	65	74 (65-86)	75 (65-91)	All cancer	47	195		1/46	9/162	47/0	191/4	8
She <i>et al</i> <sup>[30]</sup>	2013	Retro, comparative	75	80 (75-94)	80 (75-95)	All cancer	189	245	9 (4.8)	122/66	134/101	90/99	120/125	6
Scarpa <i>et al</i> <sup>[31]</sup>	2013	Retro, comparative	70	77 (74-80)	75 (72-80)	All cancer	33	24				14/19	8/16	6
Fujii <i>et al</i> <sup>[19]</sup>	2014	RCT	75	79.8 ± 3.6	80.1 ± 4.2	All cancer	100	100	3 (3)	Sep-91	85/15	50/50	60/40	NA
Hinoi <i>et al</i> <sup>[32]</sup>	2014	Retro, comparative	80	83 (81-85)	83 (81-85)	All cancer	459	459		362/107	355/104	215/244	222/237	8
Miyasaka <i>et al</i> <sup>[33]</sup>	2014	Retro, comparative	70	75 (70-86)	78 (70-94)	All cancer	28	79		6/22	48/31	13/15	27/52	6
Vallribera Valls <i>et al</i> <sup>[34]</sup>	2014	Prospective, comparative	75			All cancer	134	133		59/75	71/62	88/46	88/45	8
Zeng <i>et al</i> <sup>[35]</sup>	2015	Retro, comparative	70	74 (70-87)	74 (70-88)	Rectal cancer	112	182	7 (6.3)	66/46	92/90	62/50	98/84	6
Shigeta <i>et al</i> <sup>[36]</sup>	2015	Retro, comparative	80	82 (81-84)	83 (81-87)	All cancer	52	55	0 (0)	Apr-48	Apr-81	28/24	26/29	7

LAC: Laparoscopic surgery; OC: Open surgery; NOS: Newcastle-Ottawa scale stars.

**Figure 2** Forest plot of the mean difference for operative time. LAC: Laparoscopic surgery; OC: Open surgery.

0.0001). The heterogeneity was statistically significant (Cochrane's  $Q = 156.2123$ ,  $P < 0.0001$ ). Publication bias was not evident (Egger = 0.3993,  $P = 0.9409$ ) (Figure 2).

**Amount of estimated blood loss:** Six studies reported the amount of estimated blood loss as a mean value with standard deviation. The operation time of LAC was significantly less than OC (mean difference = -93.3738, 95%CI: -132.3437 to -54.4039,  $P < 0.0001$ ). Heterogeneity was statistically evident (Cochrane's  $Q = 74.1364$ ,  $P < 0.0001$ ). Publication bias was not evident (Egger = 0.9129,  $P = 0.7776$ ) (Figure 3).

**Mortality:** Four studies reported mortality. There was no significant difference between LAC and OC in mortality (OR = 0.5052, 95%CI: 0.2438-1.0467,  $P = 0.0662$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 2.0911$ ,  $P = 0.5537$ , Egger = -0.6646,  $P = 0.5883$ ).

**Overall morbidity:** Thirteen studies reported incidence of overall morbidity. The overall morbidity of LAC was significantly less than for OC (OR = 0.5427, 95%CI: 0.4425-0.6655,  $P < 0.0001$ ). Heterogeneity was not evident (Cochrane's  $Q = 14.7867$ ,  $P = 0.2533$ ). Publication



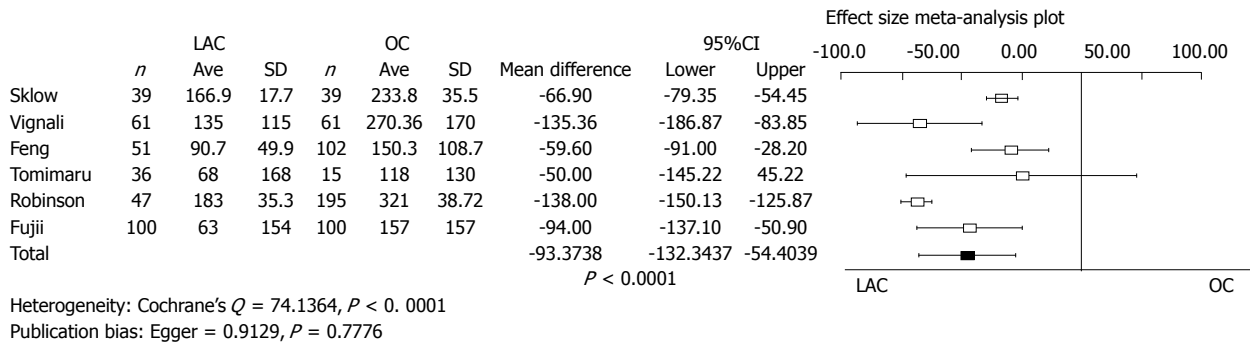


Figure 3 Forest plot of the mean difference for amount of estimated blood loss. LAC: Laparoscopic surgery; OC: Open surgery.

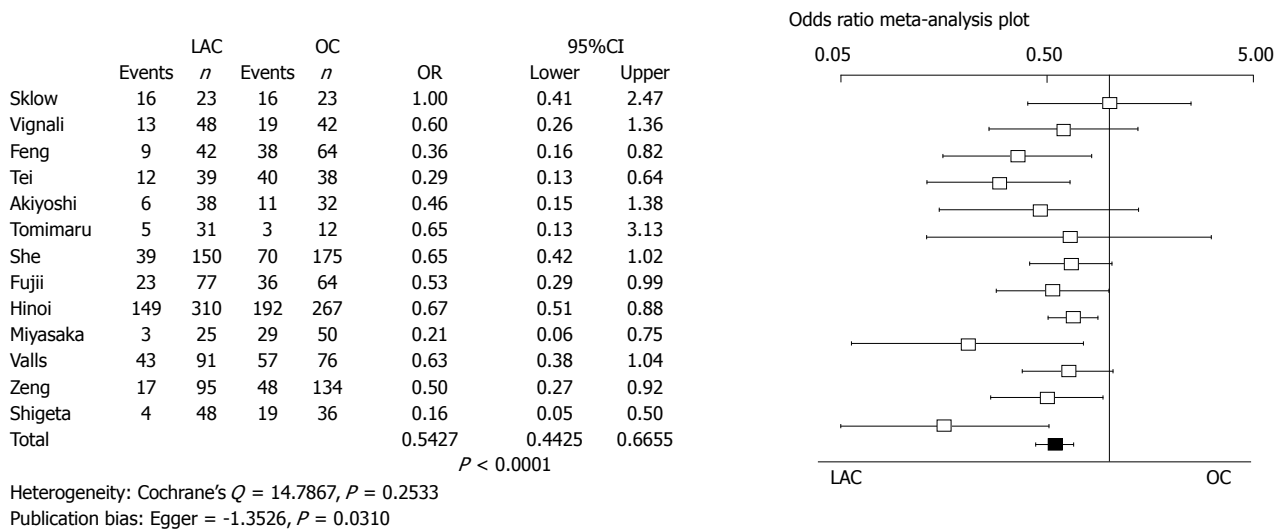


Figure 4 Forest plot of the odds ratio for overall morbidity. LAC: Laparoscopic surgery; OC: Open surgery.

bias was statistically evident (Egger = -1.3526,  $P = 0.0310$ ) (Figure 4).

**Incisional surgical site infection:** Twenty studies reported the incidence of incisional surgical site infection. The incisional surgical site infection of LAC was significantly less than for OC (OR = 0.6262, 95%CI: 0.4310-0.9097,  $P = 0.0140$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 15.2636$ ,  $P = 0.1707$ , Egger = -0.3638,  $P = 0.6557$ ) (Figure 5).

**Deep surgical site infection:** Four studies reported the incidence of deep surgical site infection. There was no significant difference between LAC and OC in deep surgical site infection (OR = 0.8234, 95%CI: 0.3298-2.0556,  $P = 0.6771$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 6.3512$ ,  $P = 0.0957$ , Egger = -3.0524,  $P = 0.1922$ ).

**Anastomotic leakage:** Twenty studies reported the incidence of anastomotic leakage. There was no significant difference between LAC and OC in anastomotic leakage (OR = 0.9138, 95%CI: 0.5667-1.4735,  $P =$

0.7115). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 8.0075$ ,  $P = 0.7126$ , Egger = 0.0396,  $P = 0.9632$ ) (Figure 6).

**Bowel obstruction and ileus:** Ten studies reported the incidence of bowel obstruction and ileus. Bowel obstruction and ileus of LAC was significantly less than for OC (OR = 0.6248, 95%CI: 0.4519-0.8638,  $P = 0.0044$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 8.7612$ ,  $P = 0.4596$ , Egger = -1.1383,  $P = 0.1602$ ) (Figure 7).

**Pneumonia:** Three studies reported the incidence of pneumonia. There was no significant difference between LAC and OC in the incidence of pneumonia (OR = 0.4526, 95%CI: 0.1976-1.0365,  $P = 0.0608$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 2.3251$ ,  $P = 0.3127$ , Egger = 0.1846,  $P = 0.9743$ ).

**Cardiovascular complication:** Eight studies reported the incidence of cardiovascular complication. Cardiovascular complications of LAC was significantly less than for OC (OR = 0.4767, 95%CI: 0.2805-0.8101,  $P = 0.0062$ ). Heterogeneity was not evident (Cochrane's  $Q$

	LAC		OC			95%CI	
	Events	<i>n</i>	Events	<i>n</i>	OR	Lower	Upper
Sklow	3	36	3	36	1.00	0.19	5.29
Vignali	5	56	9	52	0.52	0.16	1.64
Tei	4	47	25	53	0.18	0.06	0.56
Akiyoshi	3	41	2	41	1.50	0.24	9.45
Tomimaru	3	33	1	14	1.27	0.12	13.32
Robinson	9	38	38	157	0.98	0.44	2.20
She	6	183	4	241	1.98	0.55	7.10
Fujii	5	95	10	90	0.47	0.16	1.44
Hinoi	37	422	43	416	0.85	0.54	1.34
Miyasaka	1	27	10	69	0.26	0.03	2.09
Valls	4	130	10	123	0.38	0.12	1.24
Zeng	8	104	31	151	0.37	0.17	0.85
Total					0.6262	0.4310	0.9097

Heterogeneity: Cochrane's  $Q = 15.2636$ ,  $P = 0.1707$

Publication bias: Egger = -0.3638,  $P = 0.6557$

Odds ratio meta-analysis plot

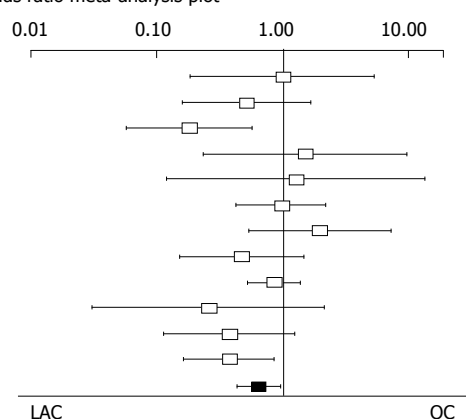


Figure 5 Forest plot of the odds ratio for incisional surgical site infection. LAC: Laparoscopic surgery; OC: Open surgery.

	LAC		OC			95%CI	
	Events	<i>n</i>	Events	<i>n</i>	OR	Lower	Upper
Vignali	4	57	3	58	1.36	0.29	6.33
Tei	2	49	2	76	1.55	0.21	11.38
Akiyoshi	1	43	2	41	0.48	0.04	5.46
Robinson	2	45	6	189	1.40	0.27	7.17
She	1	188	2	243	0.65	0.06	7.18
Scarpa	1	32	3	21	0.22	0.02	2.25
Fujii	5	95	8	92	0.61	0.19	1.92
Hinoi	8	451	2	457	4.05	0.86	19.19
Miyasaka	1	27	1	78	2.89	0.17	47.80
Valls	7	127	9	124	0.76	0.27	2.10
Zeng	2	110	6	176	0.53	0.11	2.69
Shigeta	1	51	2	53	0.52	0.05	5.91
Total					0.9138	0.5667	1.4735

Heterogeneity: Cochrane's  $Q = 8.0075$ ,  $P = 0.7126$

Publication bias: Egger = 0.0396,  $P = 0.9632$

Odds ratio meta-analysis plot

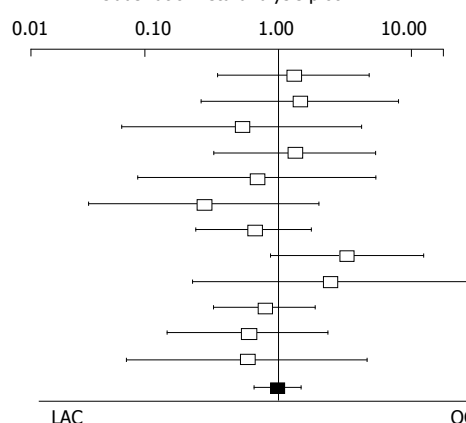


Figure 6 Forest plot of the odds ratio for anastomotic leakage. LAC: Laparoscopic surgery; OC: Open surgery.

= 6.6316,  $P = 0.4682$ ). Publication bias was statistically evident (Egger = 1.5152,  $P = 0.0521$ ) (Figure 8).

**Recovery time of normal bowel function:** Five studies reported the recovery time of normal bowel function as the mean value with standard deviation. There was no significant difference in the recovery time to normal bowel function between LAC and OC (mean difference = -0.8573, 95%CI: -1.8778 to 0.1632,  $P = 0.0997$ ). Heterogeneity was statistically evident (Cochrane's  $Q = 379.9427$ ,  $P < 0.0001$ ). Publication bias was not evident (Egger = 5.4503,  $P = 0.5226$ ).

**Length of postoperative hospital stay:** Three studies reported the length of postoperative hospital stay as mean value with standard deviation. There was no significant difference in the length of postoperative hospital stay between LAC and OC (mean difference = -1.3336, 95%CI: -3.3995 to 0.7322,  $P = 0.2058$ ).

Heterogeneity was not evident (Cochrane's  $Q = 3.9019$ ,  $P = 0.1421$ ). Publication bias was statistically evident (Egger = -1.4308,  $P = 0.0689$ ).

### Long-term outcomes

**Overall survival:** Hinoi *et al.*<sup>[32]</sup> reported overall survival in colon and rectal cancer separately. Three analyses of two studies reported the overall survival with 95%CI. There was no significant difference in the overall survival between LAC and OC (mean difference = 0.8321, 95%CI: 0.5331 to 1.2990,  $P = 0.4187$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 3.3977$ ,  $P = 0.1829$ , Egger = -1.9819,  $P = 0.3846$ ) (Figure 9).

**Disease specific survival:** Hinoi *et al.*<sup>[32]</sup> reported disease specific survival in colon and rectal cancer separately. Three analyses of two studies reported the disease specific survival with 95%CI. There was no

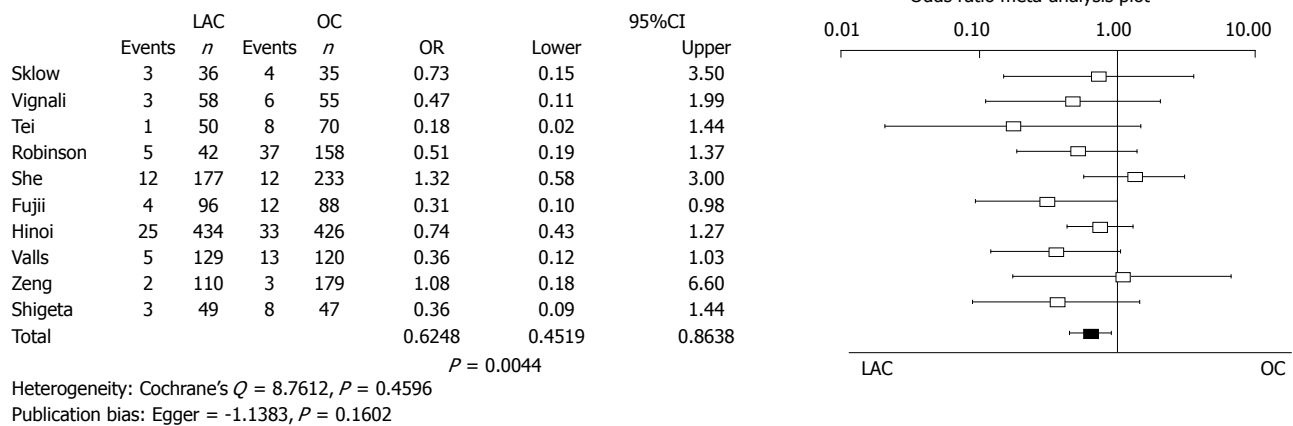


Figure 7 Forest plot of the odds ratio for bowel obstruction and ileus. LAC: Laparoscopic surgery; OC: Open surgery.

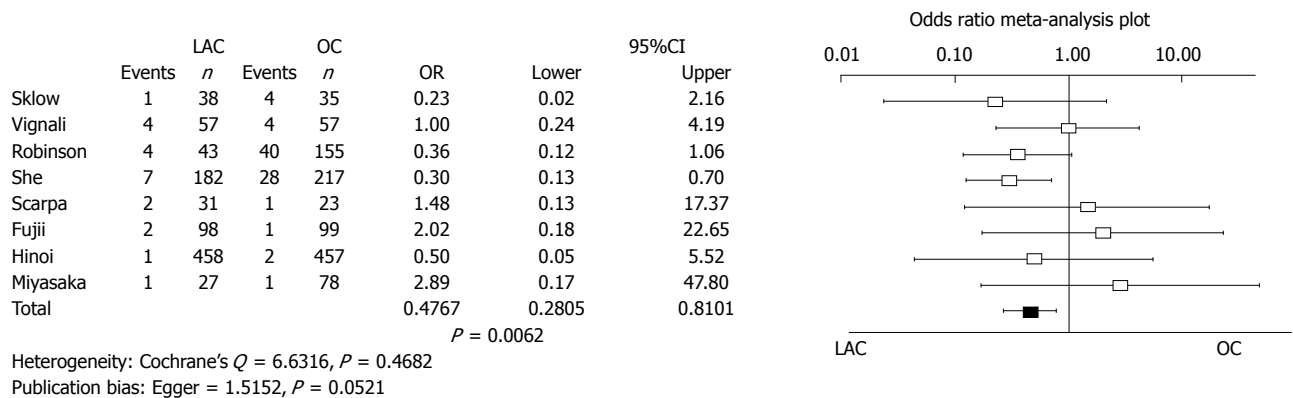


Figure 8 Forest plot of the odds ratio for cardiovascular complication. LAC: Laparoscopic surgery; OC: Open surgery.

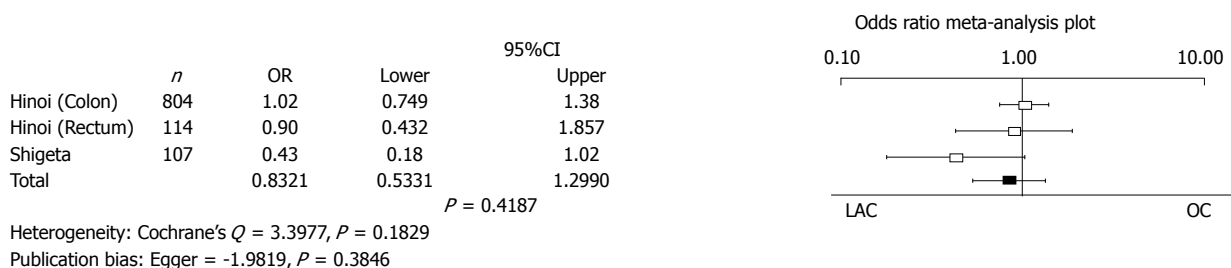


Figure 9 Forest plot of the odds ratio for overall survival. LAC: Laparoscopic surgery; OC: Open surgery.

significant difference in the disease specific survival between LAC and OC (mean difference = 1.0254, 95%CI: 0.6707 to 1.5675,  $P = 0.9209$ ). Heterogeneity and publication bias were not evident (Cochrane's  $Q = 0.1648$ ,  $P = 0.9209$ , Egger = -0.4921,  $P = 0.1559$ ) (Figure 10).

### Oncological clearance

**The number of dissected lymph nodes:** Two studies reported the number of dissected lymph nodes as the mean value with standard deviation. There was no significant difference in the number of dissected lymph nodes between LAC and OC (mean difference = -0.1360, 95%CI: -4.0553 to 3.7833,  $P = 0.9458$ ). Heterogeneity

and publication bias were not evident (Cochrane's  $Q = 3.2471$ ,  $P = 0.0716$ , Kendall tau rank correlation coefficient by Begg test = 1.0000,  $P = 0.3173$ ).

### Study quality

There was only one randomized controlled study<sup>[19]</sup> which contained the following; random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting and other potential threats to validity.

The study which had 5 or less star points on the NOS scale related to 5 short-term outcomes; amount of estimated blood loss, overall morbidity, incisional surgical site infection, anastomotic leakage and time of normal

	<i>n</i>	OR	Lower	Upper
Hinoi (Colon)	804	1.06	0.657	1.726
Hinoi (Rectum)	114	0.97	0.339	2.76
Shigeta	107	0.75	0.14	4.05
Total		1.0254	0.6707	1.5675

$P = 0.9209$

Heterogeneity: Cochrane's  $Q = 0.1648$ ,  $P = 0.9209$

Publication bias: Egger =  $-0.4921$ ,  $P = 0.1559$

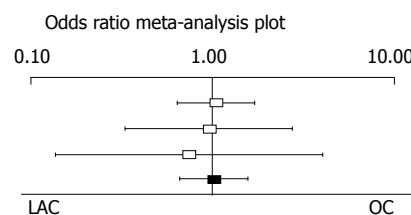


Figure 10 Forest plot of the odds ratio for disease specific survival. LAC: Laparoscopic surgery; OC: Open surgery.

bowel function. These outcomes were synthesized with studies which had 6 or more star points. Results were similar to the primary analyzed results and there was no conversion of interpretation.

## DISCUSSION

Two systematic reviews that compare LAC with OC report benefits in short-term outcome. Grailey *et al.*<sup>[11]</sup> report that LAC reduces the length of hospital stay, intraoperative blood loss, pneumonia, time to normal bowel function, cardiac complication and wound infection. Antoniou *et al.*<sup>[12]</sup> report that LAC had a decreased risk for mortality, overall morbidity, plus cardiac and respiratory complications. Their results are similar to those reported in this review. However, they included analyses for both colorectal cancer and benign disease. Large scale, randomized studies and reviews that compare long-term results between LAC and OC in all generations report no difference in colon cancer patients<sup>[37]</sup>. However, long-term results of randomized studies and reviews with elderly patient have not yet been reported. This meta-analysis, which compared LAC and OC in elderly colorectal cancer patients, demonstrates advantages in short-term and equivalency with respect to long-term outcomes and oncological clearance. These results will be useful in informing the selection of operative approach in elderly patients.

In analyses of the amount of estimated blood loss, overall morbidity, incisional surgical site infection and cardiovascular complication were all reduced in LAC. These results are similar to previous reports<sup>[11,12]</sup>. It has been suggested that decreases in blood loss and postoperative pain reduce the stress of surgery, and therefore reduce overall morbidity. The reduction in cardiovascular complications might also be due to decrease in blood loss. Bowel obstruction and ileus was also reduced in LAC. Bowel obstruction and ileus were not distinguished in this analysis, because the definition was not clear in some studies and data was assigned to both conditions. This was not shown in previous reviews and it is supposed that the incidence of ileus increase is due to the extent of lymph node dissection in colorectal cancer. The exposure of intestines and major trauma to the abdominal wall might explain the increase in incidence of bowel paralysis and adhesion in OC.

The operative time of LAC was longer than OC. This

result was consistent with past reports, too. However, pneumonia was not increased and overall morbidity was decreased in LAC. Mean difference in operative time was about 34 min. The increase in operative time and pneumoperitoneum may not cause adverse effects on postoperative morbidity.

In this meta-analysis, there were no significant differences in mortality, incidence of pneumonia and recovery time of normal bowel function, which is not consistent with past reports. However, all LAC results tended to be lower than OC and p-values were close to being significantly different (mortality; OR = 0.5052, 95%CI: 0.2438- 1.0467,  $P = 0.0662$ , pneumonia; OR = 0.4526, 95%CI: 0.1976-1.0365,  $P = 0.0608$ , recovery time of normal bowel function; mean difference =  $-0.8573$ , 95%CI:  $-1.8778$  to  $0.1632$ ,  $P = 0.0997$ ). These inconsistent results may be due to the fact that patients who underwent elective colorectal surgery could be considered to be at relatively low risk. The reason for there being no significant difference in recovery time of normal bowel function is unknown. There might have been a significant difference if the time period of the data collection was a number of days not hours.

The incidences of deep surgical site infection and anastomotic leakage were similar between LAC and OC (deep surgical site infection; OR = 0.8234, 95%CI: 0.3298-2.0556,  $P = 0.6771$ , anastomotic leakage; OR = 0.9138, 95%CI: 0.5667-1.4735,  $P = 0.7115$ ). It has been suggested that surgical invasiveness of the retroperitoneal dissection and anastomotic procedure are similar between LAC and OC in colorectal cancer surgery.

There was no significant difference in length of postoperative hospital stay.

This may be due to differences in the standard for hospital discharge in each study and may also be related to differences in the insurance systems in each country. Thus there might be a large bias in social factors between studies.

In analyses of long-term outcomes, both overall and disease specific survival rates were similar. There was also no significant difference in the number of dissected lymph nodes. This reveals the fact that LAC had similar treatment success to OC. The results of randomized studies and Cochrane review were also supported by this meta-analysis in elderly colorectal cancer surgery

patients<sup>[13-18,37]</sup>.

The limitation of this review is that it consists of only one randomized controlled study. Thus there were publication biases in analyses of overall morbidity, cardiovascular complication and length of postoperative hospital stay. Analysis of high risk elderly patients with impaired cardiac and pulmonary function might be required in the future. A secondary limitation of this study is that long-term outcomes were limited to three data sets from two studies. The analysis of more long-term results, that include details on the specific form of relapse, may thus be required.

LAC in elderly colorectal cancer patients had benefits in short-term outcomes such as amount of estimated blood loss, overall morbidity, incidences of incisional surgical site infection, bowel obstruction and ileus and cardiovascular complications. The only area where LAC did not show a benefit over OC was for operative time. The long-term outcomes and oncological clearance of LAC were similar to that of OC. These results support the view that LAC is an effective and safe procedure for elderly patients with colorectal cancer.

## COMMENTS

### Background

Laparoscopic surgery for colorectal cancer is increasing rapidly, particularly among elderly patients. However, neither the safety nor the effectiveness of laparoscopic surgery in this demographic has yet been determined.

### Research frontiers

Some systematic reviews that compare laparoscopic colectomy (LAC) with open colectomy for elderly had reported benefits in short-term outcome.

### Innovations and breakthroughs

However, past reports included benign diseases, and no report about long-term results. The authors analyzed for elderly colorectal cancer only and long-term outcomes.

### Applications

Some short-term outcomes were superior in LAC except operation time. There was no significant difference in long-term outcomes. LAC is an effective procedure for elderly with colorectal cancer.

### Terminology

LAC: Laparoscopic colectomy.

### Peer-review

Good review article, scientific and rigorous analysis.

## REFERENCES

- 1 **World Health Organization.** Men, ageing and health: Achieving health across the life span. [World Health Organization web site]. Available from: URL: [http://whqlibdoc.who.int/hq/2001/WHO\\_NM\\_H\\_NPH\\_01.2.pdf?ua=1](http://whqlibdoc.who.int/hq/2001/WHO_NM_H_NPH_01.2.pdf?ua=1)
- 2 **Rasool S, Kadla SA, Rasool V, Ganai BA.** A comparative overview of general risk factors associated with the incidence of colorectal cancer. *Tumour Biol* 2013; **34**: 2469-2476 [PMID: 23832537 DOI: 10.1007/s13277-013-0876-y]
- 3 **Frasson M, Braga M, Vignali A, Zuliani W, Di Carlo V.** Benefits of laparoscopic colorectal resection are more pronounced in elderly patients. *Dis Colon Rectum* 2008; **51**: 296-300 [PMID: 18197453 DOI: 10.1007/s10350-007-9124-0]
- 4 **Senagore AJ, Madbouly KM, Fazio VW, Duepre HJ, Brady KM, Delaney CP.** Advantages of laparoscopic colectomy in older patients. *Arch Surg* 2003; **138**: 252-256 [PMID: 12611568 DOI: 10.1001/archsurg.138.3.252]
- 5 **Manceau G, Karoui M, Werner A, Mortensen NJ, Hannoun L.** Comparative outcomes of rectal cancer surgery between elderly and non-elderly patients: a systematic review. *Lancet Oncol* 2012; **13**: e525-e536 [PMID: 23182193 DOI: 10.1016/s1470-2045(12)70378-9]
- 6 **Tuech JJ, Pessaix P, Rouge C, Regenet N, Bergamaschi R, Arnaud JP.** Laparoscopic vs open colectomy for sigmoid diverticulitis: a prospective comparative study in the elderly. *Surg Endosc* 2000; **14**: 1031-1033 [PMID: 11116412 DOI: 10.1007/s004640000267]
- 7 **Stocchi L, Nelson H, Young-Fadok TM, Larson DR, Ilstrup DM.** Safety and advantages of laparoscopic vs. open colectomy in the elderly: matched-control study. *Dis Colon Rectum* 2000; **43**: 326-332 [PMID: 10733113 DOI: 10.1007/BF02258297]
- 8 **Stewart BT, Stitz RW, Lumley JW.** Laparoscopically assisted colorectal surgery in the elderly. *Br J Surg* 1999; **86**: 938-941 [PMID: 10417569 DOI: 10.1046/j.1365-2168.1999.01160.x]
- 9 **Lian L, Kalady M, Geisler D, Kiran RP.** Laparoscopic colectomy is safe and leads to a significantly shorter hospital stay for octogenarians. *Surg Endosc* 2010; **24**: 2039-2043 [PMID: 20174947 DOI: 10.1007/s00464-010-0900-x]
- 10 **Law WL, Chu KW, Tung PH.** Laparoscopic colorectal resection: a safe option for elderly patients. *J Am Coll Surg* 2002; **195**: 768-773 [PMID: 12495308 DOI: 10.1016/S1072-7515(02)01483-7]
- 11 **Grailey K, Markar SR, Karthikesalingam A, Aboud R, Ziprin P, Faiz O.** Laparoscopic versus open colorectal resection in the elderly population. *Surg Endosc* 2013; **27**: 19-30 [PMID: 22752280 DOI: 10.1007/s00464-012-2414-1]
- 12 **Antoniu SA, Antoniu GA, Koch OO, Pointner R, Granderath FA.** Laparoscopic colorectal surgery confers lower mortality in the elderly: a systematic review and meta-analysis of 66,483 patients. *Surg Endosc* 2015; **29**: 322-333 [PMID: 24986017 DOI: 10.1007/s00464-014-3672-x]
- 13 **Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, Brown JM.** Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. *Br J Surg* 2013; **100**: 75-82 [PMID: 23132548 DOI: 10.1002/bjs.8945]
- 14 **Lacy AM, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, Pique JM.** The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg* 2008; **248**: 1-7 [PMID: 18580199 DOI: 10.1097/SLA.0b013e31816a9d65]
- 15 **Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, Hellinger M, Flanagan R, Peters W, Nelson H.** Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007; **246**: 655-662; discussion 662-664 [PMID: 17893502 DOI: 10.1097/sla.0b013e318155a762]
- 16 **Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Pahlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ.** Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009; **10**: 44-52 [PMID: 19071061 DOI: 10.1016/S1470-2045(08)70310-3]
- 17 **Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Hon SS.** Long-term morbidity and oncologic outcomes of laparoscopic-assisted anterior resection for upper rectal cancer: ten-year results of a prospective, randomized trial. *Dis Colon Rectum* 2009; **52**: 558-566 [PMID: 19404053 DOI: 10.1007/DCR.0b013e31819ec20c]
- 18 **Morris EJ, Jordan C, Thomas JD, Cooper M, Brown JM, Thorpe H, Cameron D, Forman D, Jayne D, Quirke P.** Comparison of treatment and outcome information between a clinical trial and the National Cancer Data Repository. *Br J Surg* 2011; **98**: 299-307 [PMID: 20981742 DOI: 10.1002/bjs.7295]
- 19 **Fujii S, Ishibe A, Ota M, Yamagishi S, Watanabe K, Watanabe J,**



- Kanazawa A, Ichikawa Y, Oba M, Morita S, Hashiguchi Y, Kunisaki C, Endo I. Short-term results of a randomized study between laparoscopic and open surgery in elderly colorectal cancer patients. *Surg Endosc* 2014; **28**: 466-476 [PMID: 24122242 DOI: 10.1007/s00464-013-3223-x]
- 20 **Higgins JPT**, Green S. Assessing risk of bias in included studies Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011] The Cochrane Collaboration, 2011. [accessed 2015 May 12]. Available from: URL: <http://handbook.cochrane.org>
  - 21 **Wells GA**, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital/Research Institute web site, 2003. [accessed 2015 May 12]. Available from: URL: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
  - 22 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]
  - 23 **Sklow B**, Read T, Birnbaum E, Fry R, Fleshman J. Age and type of procedure influence the choice of patients for laparoscopic colectomy. *Surg Endosc* 2003; **17**: 923-929 [PMID: 12618937 DOI: 10.1007/s00464-002-8949-9]
  - 24 **Vignali A**, Di Palo S, Tamburini A, Radaelli G, Orsenigo E, Staudacher C. Laparoscopic vs. open colectomies in octogenarians: a case-matched control study. *Dis Colon Rectum* 2005; **48**: 2070-2075 [PMID: 16086219 DOI: 10.1007/s10350-005-0147-0]
  - 25 **Feng B**, Zheng MH, Mao ZH, Li JW, Lu AG, Wang ML, Hu WG, Dong F, Hu YY, Zang L, Li HW. Clinical advantages of laparoscopic colorectal cancer surgery in the elderly. *Aging Clin Exp Res* 2006; **18**: 191-195 [PMID: 16804364 DOI: 10.1007/BF03324648]
  - 26 **Tei M**, Ikeda M, Haraguchi N, Takemasa I, Mizushima T, Ishii H, Yamamoto H, Sekimoto M, Doki Y, Mori M. Postoperative complications in elderly patients with colorectal cancer: comparison of open and laparoscopic surgical procedures. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 488-492 [PMID: 20027093 DOI: 10.1097/SLE.0b013e3181bd9562]
  - 27 **Akiyoshi T**, Kuroyanagi H, Oya M, Konishi T, Fukuda M, Fujimoto Y, Ueno M, Yamaguchi T. Short-term outcomes of laparoscopic rectal surgery for primary rectal cancer in elderly patients: is it safe and beneficial? *J Gastrointest Surg* 2009; **13**: 1614-1618 [PMID: 19582517 DOI: 10.1007/s11605-009-0961-0]
  - 28 **Tomimaru Y**, Ide Y, Murata K. Outcome of laparoscopic surgery for colon cancer in elderly patients. *Asian J Endosc Surg* 2011; **4**: 1-6 [PMID: 22776166 DOI: 10.1111/j.1758-5910.2010.00061.x]
  - 29 **Robinson CN**, Balentine CJ, Marshall CL, Wilks JA, Anaya D, Artinyan A, Berger DH, Albo D. Minimally invasive surgery improves short-term outcomes in elderly colorectal cancer patients. *J Surg Res* 2011; **166**: 182-188 [PMID: 21276980 DOI: 10.1016/j.jss.2010.05.053]
  - 30 **She WH**, Poon JT, Fan JK, Lo OS, Law WL. Outcome of laparoscopic colectomy for cancer in elderly patients. *Surg Endosc* 2013; **27**: 308-312 [PMID: 22820704 DOI: 10.1007/s00464-012-2466-2]
  - 31 **Scarpa M**, Di Cristofaro L, Cortinovis M, Pinto E, Massa M, Alfieri R, Cagol M, Saadeh L, Costa A, Castoro C, Bassi N, Ruffolo C. Minimally invasive surgery for colorectal cancer: quality of life and satisfaction with care in elderly patients. *Surg Endosc* 2013; **27**: 2911-2920 [PMID: 23468328 DOI: 10.1007/s00464-013-2854-2]
  - 32 **Hinoi T**, Kawaguchi Y, Hattori M, Okajima M, Ohdan H, Yamamoto S, Hasegawa H, Horie H, Murata K, Yamaguchi S, Sugihara K, Watanabe M. Laparoscopic versus open surgery for colorectal cancer in elderly patients: a multicenter matched case-control study. *Ann Surg Oncol* 2015; **22**: 2040-2050 [PMID: 25331007 DOI: 10.1245/s10434-014-4172-x]
  - 33 **Miyasaka Y**, Mochidome N, Kobayashi K, Ryu S, Akashi Y, Miyoshi A. Efficacy of laparoscopic resection in elderly patients with colorectal cancer. *Surg Today* 2014; **44**: 1834-1840 [PMID: 24121951 DOI: 10.1007/s00595-013-0753-8]
  - 34 **Vallribera Valls F**, Landi F, Espin Basany E, Sánchez García JL, Jiménez Gómez LM, Martí Gallostra M, Salgado Cruz L, Armengol Carrasco M. Laparoscopy-assisted versus open colectomy for treatment of colon cancer in the elderly: morbidity and mortality outcomes in 545 patients. *Surg Endosc* 2014; **28**: 3373-3378 [PMID: 24928231 DOI: 10.1007/s00464-014-3597-4]
  - 35 **Zeng WG**, Zhou ZX, Hou HR, Liang JW, Zhou HT, Wang Z, Zhang XM, Hu JJ. Outcome of laparoscopic versus open resection for rectal cancer in elderly patients. *J Surg Res* 2015; **193**: 613-618 [PMID: 25214259 DOI: 10.1016/j.jss.2014.08.012]
  - 36 **Shigeta K**, Baba H, Yamafuji K, Asami A, Takeshima K, Nagasaki K, Okamoto N, Murata T, Arai S, Kubochi K, Kitagawa Y. Effects of laparoscopic surgery on the patterns of death in elderly colorectal cancer patients: competing risk analysis compared with open surgery. *Surg Today* 2016; **46**: 422-429 [PMID: 25904559 DOI: 10.1007/s00595-015-1171-x]
  - 37 **Kuhry E**, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* 2008; **(2)**: CD003432 [PMID: 18425886 DOI: 10.1002/14651858]

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