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IMPACTO DE LAS COMPLICACIONES POSTOPERATORIAS Y EL ESTADO INFLAMATORIO EN EL PRONÓSTICO DEL CÁNCER COLORRECTAL

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INDICE

1. INTRODUCCIÓN

1.1. Aspectos generales del cáncer colorrectal

El cáncer colorrectal (CCR) es uno de los cánceres más frecuentes a nivel mundial, ocupando el tercer lugar en incidencia. Se estima que se diagnosticarán 2.048.108 casos en 2025, tratándose del segundo cáncer en mortalidad, con unas 961.485 muertes por esta causa en el presente año[1]. En nuestro país, la Red Española de Registros de Cáncer señaló que en 2024 se diagnosticaron 44.294 nuevos casos y en los últimos datos de 2022, las defunciones por cáncer de colon, recto o ano ascendieron a 15.198 casos[2].

La incidencia y mortalidad son variables entre diferentes países debido a factores como la edad, el sexo y la raza[3]. Las mayores incidencias se registran en los países desarrollados, debido a factores dietéticos y de estilo de vida, aunque en los últimos años se ha observado un aumento en el número de casos en países menos desarrollados en relación con una integración de estos factores de riesgo propios de los países con mayor incidencia de CCR[4].

Existen ciertos factores de riesgo no modificables que aumentan la incidencia de CCR, como la edad, el sexo y la presencia de algunas enfermedades. El más relevante es la edad: el 70% de los pacientes con CCR se diagnostican por encima de los 65 años[5]. El diagnóstico en menores de 40 años es muy poco frecuente, aunque la incidencia en este grupo de población está aumentando debido a los cambios en el estilo de vida[6]. También se encuentran diferencias en ambos sexos, siendo un 25% más incidente en hombres[5], aunque algunos estudios han mostrado que el cáncer de colon derecho es más frecuente en mujeres[7].

La raza se reconoce como un factor de riesgo no modificable en la epidemiología del cáncer colorrectal, observándose diferencias significativas en términos de incidencia, mortalidad y características clínicas entre distintos grupos raciales y étnicos. En Estados Unidos, tanto la población afroamericana como la nativoamericana presentan tasas más elevadas de incidencia y mortalidad en comparación con otros grupos, con diferencias en la supervivencia global que superan el 5%. Específicamente, los pacientes afroamericanos suelen ser diagnosticados a edades más tempranas y en estadios más avanzados de la enfermedad. Estas disparidades tienen un origen multifactorial, en el que confluyen factores socioeconómicos, posibles diferencias en la biología tumoral y desigualdades estructurales dentro del sistema sanitario[3].

Los factores genéticos desempeñan un papel fundamental en la etiopatogenia del CCR. Entre los síndromes hereditarios más prevalentes se encuentran la poliposis adenomatosa familiar y el síndrome de Lynch, los cuales conllevan un riesgo estimado de desarrollar la enfermedad cercano al 100% y entre el 50% y el 80%, respectivamente, en ausencia de intervención preventiva o tratamiento específico[8].

Algunas enfermedades pueden predisponer al desarrollo de CCR, como la diabetes tipo 2 que aumenta hasta en un 30% el riesgo[9]. Otra patología más claramente relacionada con el CCR es la enfermedad inflamatoria intestinal: estos pacientes presentan un riesgo de 2 a 6[10] veces mayor a la población general de ser diagnosticados de CCR a lo largo de su vida, adelantándose su aparición unos 7,7 años respecto al resto de la población, asociándose además a un peor pronóstico[11]. Tanto en la enfermedad de Crohn como en la colitis ulcerosa existe un aumento del riesgo de cáncer de colon, mientras que la relación con el cáncer de recto está más establecida en la colitis ulcerosa[12]. De estos hallazgos se deduce la importancia del *screening* precoz endoscópico en pacientes con enfermedad inflamatoria intestinal en edades tempranas, con el objetivo de disminuir la mortalidad en este grupo[10].

En cuanto a los factores de riesgo modificables se ha observado que un consumo elevado de carne roja (50g al día) aumenta el riesgo de cáncer colorrectal un 17%[13]. Un riesgo similar, entorno al 15%, se ha atribuido al consumo de tabaco[14], bebidas azucaradas[15] y al consumo moderado de alcohol. El riesgo de este último se eleva hasta el 40% en pacientes con consumo elevado de alcohol (>50g diarios)[16]. Algunos estudios han encontrado que un aporte elevado de vitamina D y calcio disminuye el riesgo de CCR[17,18].

Actualmente, la cirugía sigue siendo el pilar fundamental del tratamiento del cáncer colorrectal. La resección quirúrgica completa del tumor, con márgenes libres, y una linfadenectomía extensa, ofrecen la mejor oportunidad de curación y es fundamental para obtener un control local de la enfermedad[19].

Otros pilares del tratamiento son la quimioterapia y la radioterapia, que contribuyen de forma significativa a mejorar la supervivencia global y libre de enfermedad, dependiendo del estadio y localización tumoral.

La quimioterapia tiene un papel central tanto en la enfermedad localizada como en la metastásica. En etapas localizadas, la quimioterapia adyuvante mejora la supervivencia en pacientes con enfermedad de alto riesgo, especialmente en estadio III y algunos casos seleccionados de estadio II, con un beneficio absoluto en supervivencia

a 5 años de aproximadamente 5%[20]. En enfermedad metastásica, la quimioterapia sistémica prolonga la supervivencia y puede convertir metástasis inicialmente irresecables en resecables, permitiendo potenciales curas en una minoría de pacientes[21].

La radioterapia es fundamental en el manejo del cáncer de recto localmente avanzado, donde se utiliza en el contexto neoadyuvante, sola o combinada con quimioterapia, para reducir la recurrencia local y mejorar la posibilidad de resección completa[22]. En cáncer de colon, la radioterapia tiene un papel muy limitado, reservándose para casos con invasión local extensa o márgenes positivos tras cirugía[23].

A pesar de los avances en las técnicas quirúrgicas, la quimioterapia adyuvante y las terapias dirigidas, el pronóstico del CCR sigue siendo incierto en muchos casos, especialmente en etapas intermedias y avanzadas.

1.2. Pronóstico del cáncer colorrectal

El pronóstico del CCR es multifactorial y debe evaluarse en función de una serie de variables clínicas, histológicas y moleculares para una adecuada estratificación y manejo individualizado. Es por ello por lo que se han descrito numerosos factores pronósticos relacionados con la supervivencia del CCR.

La clasificación TNM establecida por la *American Joint Comittee on Cancer* (AJCC) constituye el principal factor pronóstico del CCR[24]. Su validez radica en su capacidad para estratificar a los pacientes en grupos según la situación de la enfermedad al diagnóstico, integrando tres dimensiones patológicas clave[25]:

- **T (profundidad de la invasión):** los tumores T1-T2 (limitados a la capa mucosa/submucosa o muscular propia – estadio I) presentan supervivencias a los 5 años de hasta el 95%, mientras que, en los más avanzados, T3-T4 (afectación de la capa serosa o invasión de otros órganos – estadio II) la supervivencia disminuye hasta el 60-70%.
- **N (afectación ganglionar):** la presencia de células tumorales en los ganglios linfáticos regionales (estadio III) disminuye drásticamente la supervivencia a 5 años, siendo del 65% cuando la afectación es de 1-3 ganglios y cayendo hasta el 35% cuando la afectación es mayor.

- **M (afectación de órganos a distancia):** el estadio IV supone el de peor pronóstico de la enfermedad, con supervivencias medias de 18 meses. En casos seleccionados de enfermedad oligometastásica (hepáticas o pulmonares únicas) se pueden alcanzar supervivencias del 30-50% a 5 años tras terapias multimodales.

En la siguiente tabla observan las diferencias en supervivencia según el estadio tumoral basado en la 8ª edición de la clasificación TNM[24,25]:

ESTADIO	T (Tumor)	N (Ganglios)	M (Metástasis)	Supervivencia a 5 años
0	Tis	N0	M0	>95%
I	T1-T2	N0	M0	90-95%
IIA	T3	N0	M0	80-85%
IIB	T4a	N0	M0	75-80%
IIC	T4b	N0	M0	60-65%
IIIA	T1-T2 T1	N1 N2a	M0 M0	70-75%
IIIB	T1-T2 T2-T3 T3-T4a	N2b N2a N1	M0 M0 M0	40-60%
IIIC	T3-T4a T4a T4b	N2b N2a N+	M0 M0 M0	25-30%
IVA	Cualquier T	Cualquier N	M1a	20-25%
IVB	Cualquier T	Cualquier N	M1b	10-15%
IVC	Cualquier T	Cualquier N	M1c	5%

Pese a su inestimable utilidad para estratificar a los pacientes según el estadio de la enfermedad y su pronóstico, la clasificación TNM presenta algunas limitaciones, como aquellos pacientes estadio III/IV irresecables de inicio que tras tratamiento médico con quimio y/o radioterapia y se convierten en resecables, modificando el pronóstico independientemente del TNM inicial. Otra limitación es que esta clasificación no integra muchos otros factores biológicos, clínicos y analíticos que se han relacionado con el pronóstico de la enfermedad[26].

Los factores biológicos más ampliamente estudiados son los siguientes:

- **Localización tumoral:** el cáncer de colon derecho presenta peor pronóstico que el localizado a nivel izquierdo[27], particularmente en los estadios avanzados III y IV[28]. Estas diferencias se deben a diferentes factores:
    - Origen embrionario: el colon derecho deriva del intestino primitivo medio y el izquierdo del primitivo posterior, implicando diferencias en biología celular, vascularización y expresión génica.
    - Moleculares y genéticos: el colon derecho presenta mayor frecuencia de inestabilidad de microsatélites y mutaciones de BRAF, mientras que el colon izquierdo presenta mutaciones más frecuentes en KRAS y TP53, asociado a tumores más diferenciados[29].
    - Microambiente tumoral: diferencias en la microbiota entre colon derecho e izquierdo que pueden variar el entorno inmunológico entre una zona y otra, así como la presencia de factores inflamatorios que pueden favorecer el desarrollo tumoral[30].
    - Presentación clínica: el colon derecho se diagnostica más tardíamente por un crecimiento más silente y síntomas más inespecíficos, mientras que el colon izquierdo presenta síntomas tempranos como cambios en el ritmo deposicional y/o sangrado, que propician un diagnóstico más temprano.
- **Invasión linfovascular:** es la presencia de células tumorales dentro de vasos linfáticos o sanguíneos, identificada histopatológicamente en la pieza quirúrgica. Su hallazgo indica que el tumor ha adquirido la capacidad de diseminarse más allá del sitio primario a través de los vasos, lo que representa un paso temprano en el proceso metastásico. Con una incidencia entre el 5 y el 30% se asocia de manera independiente con un pronóstico desfavorable[31]. Se correlaciona además con un mayor grado histológico y estadios avanzados, así como mayor riesgo de recurrencia local y sistémica y menor supervivencia global y libre de enfermedad, tanto en etapas tempranas como avanzadas de la enfermedad[32]. Concretamente la invasión vascular extramural se relaciona con un peor pronóstico[33].
- **Invasión perineural:** se asocia de manera independiente con un pronóstico desfavorable. Se correlaciona con un mayor riesgo de recurrencia local, menor supervivencia global y libre de enfermedad, independientemente de otros factores pronósticos[34]. Diversos estudios y metaanálisis han demostrado que su impacto es comparable al de la afectación ganglionar. En pacientes con enfermedad estadio II, la supervivencia de quienes presentan invasión perineural es similar a la de pacientes con estadio III, lo que ha

llevado a considerar la presencia de este factor como criterio de alto riesgo para indicar quimioterapia adyuvante[35].

- **Gemación o *budding* tumoral:** es un hallazgo histopatológico que describe la presencia de pequeños grupos de células tumorales que se desprenden del tumor principal y se infiltran en el tejido conectivo adyacente. Se considera que este hecho facilita la diseminación tumoral al adquirir las células características más móviles e invasivas. Se ha descrito como factor independiente predictor de progresión de la enfermedad y de muerte por cáncer[36].
- **Grado de diferenciación tumoral:** constituye un factor pronóstico adverso independiente del estadio en el cáncer colorrectal, un mayor grado tumoral se asocia a una menor supervivencia libre de enfermedad, menor supervivencia específica por cáncer y un mayor riesgo de recurrencia[37]. Un grado tumoral alto suele relacionarse con un estadio más avanzado, mayor profundidad de invasión tumoral, afectación ganglionar e invasión linfovascular[38].
- **Marcadores moleculares:**
    - *BRAF:* La mutación de este biomarcador es más frecuente en mujeres y pacientes de mayor edad y se asocia con tumores peor diferenciados, mucinosos y de localización en colon proximal[39]. Está claramente establecido que es un factor de mal pronóstico en la enfermedad metastásica. Mientras que en estadio I se ha visto que el BRAF mutado no influye en el pronóstico, existe mayor controversia sobre los estadios II-III[38].
    - *KRAS y NRAS:* siendo más frecuente el primero, la mutación de estos marcadores se relaciona con una ausencia de regulación en el crecimiento del tumor y es un predictor de resistencia a terapias anti-EGFR[40,41]. Mientras que en la enfermedad metastásica se han relacionado con un peor pronóstico[42], no está tan establecida esta relación en los estadios previos[38].
- **Marcadores tumorales:**
    - *Antígeno carcinoembrionario (CEA, por sus siglas en inglés):* es una glicoproteina cuya elevación en sangre se ha asociado a mayor agresividad tumoral en el CCR. Múltiples estudios han mostrado que niveles elevados de CEA al diagnóstico se relacionan con una peor supervivencia global y especifica, incluso en pacientes sin afectación ganglionar ni a distancia[43-46].

- *Antígeno Carbohidratado 19.9 (CA19.9, por sus siglas en inglés):* clásicamente relacionado con el cáncer pancreatobiliar, también se ha relacionado con una mayor carga tumoral, presencia de metástasis y peor supervivencia en el CCR, especialmente cuando se combina con niveles elevados de CEA. Se trata de un marcador de expresión variable en la población, que se puede alterar en patología benigna y con menor especificidad que el CEA, por lo que se recomienda que sea de uso complementario a este[47,48].

Recientemente, teniendo en cuenta el envejecimiento poblacional, se ha demostrado cierta implicación de factores relacionados con el paciente:

- **Edad:** los pacientes de mayor edad presentan peor supervivencia global y especifica en comparación con los pacientes más jóvenes. Este peor pronóstico se asume por la comorbilidad de los pacientes, por una mayor morbimortalidad postoperatoria y por una menor utilización de tratamientos oncológicos (quimioterapia y radioterapia)[49].
- **Sexo:** clásicamente se ha identificado como un factor de riesgo, siendo las mujeres las que presentan un mejor pronóstico, especialmente las diagnosticadas antes de los 65 años y con enfermedad localizada. Esta ventaja se atribuye, entre otros, al factor protector de los estrógenos endógenos y por la presencia de perfiles inmunológicos asociados a mejor pronóstico[50]. Sin embargo, estudios más recientes no han encontrado diferencias en supervivencia entre ambos sexos[51].
- **Comorbilidad:** es un factor pronóstico independiente de supervivencia global y específica en CCR. Las comorbilidades, evaluadas mediante escalas como el índice de Charlson se asocian con mayor morbimortalidad, menor probabilidad de recibir tratamientos adyuvantes y mayor riesgo de complicaciones postoperatorias[52,53]. Existe evidencia que relaciona la presencia de comorbilidades con un diagnóstico tardío, sobretodo en pacientes con enfermedades crónicas[54].
- **Fragilidad:** se asocia con un peor pronóstico en pacientes con CCR, tanto en supervivencia como morbimortalidad postoperatoria[55]. La literatura respalda que la fragilidad, evaluada mediante escalas como la *Clinical Frailty Scale* o el *Frailty Index*, es un marcador pronóstico relevante en CCR[56].

La mayoría de factores pronósticos previamente descritos, a excepción de los relacionados propiamente con el paciente, presentan ciertas limitaciones para la estratificación del riesgo al momento del diagnóstico. La más relevante es que la mayoría de ellos no pueden determinarse hasta después de la cirugía. Además, algunos parámetros, como los marcadores moleculares, pueden implicar un coste elevado y no estar disponibles en todos los entornos sanitarios.

Por este motivo, investigaciones recientes se han dirigido a considerar otros posibles marcadores pronósticos, más asequibles y de menor coste, que han sido clásicamente menos estudiados. Por una parte, cabe considerar el estado inflamatorio del paciente, medido mediante parámetros inflamatorios obtenidos en un análisis de sangre y, por otra parte, la evolución en el postoperatorio tras la cirugía por CCR, es decir, la aparición de complicaciones postoperatorias.

1.3. Estado inflamatorio

La relación entre inflamación y cáncer ha sido objeto de estudio desde hace más de un siglo. Ya en 1863, Rudolf Virchow propuso que los procesos inflamatorios crónicos podían favorecer la aparición de tumores, al observar infiltrados leucocitarios en tejido tumoral. Desde entonces, se ha consolidado la evidencia que demuestra que la inflamación no solo participa en las fases iniciales de la carcinogénesis, sino que también desempeña un papel central en la progresión, angiogénesis, invasión y metástasis de múltiples tipos de cáncer, incluido el CCR[57].

El CCR es un claro ejemplo de neoplasia en la que la inflamación está implicada en su origen y evolución. Las enfermedades inflamatorias intestinales crónicas, como la colitis ulcerosa y la enfermedad de Crohn, aumentan significativamente el riesgo de desarrollar CCR, lo que refuerza el vínculo etiopatogénico entre inflamación persistente y transformación neoplásica[10]. A nivel molecular, los procesos inflamatorios contribuyen a la producción de radicales libres de oxígeno y nitrógeno que causan daño al ADN, activación de oncogenes, inhibición de genes supresores tumorales y alteración del microambiente tisular[58].

Durante el desarrollo tumoral, las células malignas pueden inducir un estado inflamatorio sistémico mediante la secreción de citocinas proinflamatorias, como la interleucina-6 (IL-6), el factor de necrosis tumoral alfa (TNF-α) o la proteína C reactiva (PCR). Este estado inflamatorio puede suprimir la inmunidad antitumoral, favorecer la

angiogénesis y facilitar la diseminación metastásica[59]. En consecuencia, la respuesta inflamatoria sistémica del paciente se ha convertido en una variable de interés como potencial marcador de pronóstico.

La medición indirecta de este estado inflamatorio mediante parámetros analíticos accesibles ha cobrado especial relevancia en los últimos años. Marcadores como la PCR, el índice plaqueta-linfocito (IPL) y el índice neutrófilo-linfocito (INL) han sido objeto de múltiples estudios que apuntan a su utilidad tanto para predecir complicaciones postoperatorias como para estimar la supervivencia a largo plazo en pacientes con CCR[60].

Estas observaciones han impulsado un cambio en la concepción del pronóstico oncológico, pasando de una visión centrada exclusivamente en el tumor a un enfoque más integral que contempla la interacción entre el tumor y el paciente. En este nuevo marco, la inflamación sistémica se perfila como un componente clave que puede ofrecer información adicional y complementaria a la estadificación tradicional.

La progresión del cáncer colorrectal no depende exclusivamente de las características intrínsecas del tumor, sino también de su interacción con el sistema inmunitario del huésped y el entorno inflamatorio sistémico. En este contexto, se ha demostrado que ciertos parámetros inflamatorios, fácilmente accesibles mediante análisis de laboratorio rutinarios, pueden reflejar el equilibrio entre mecanismos proinflamatorios y antitumorales.

La **Proteína C Reactiva** se sintetiza en el hígado en respuesta a Interleucina-6, TNF-α e IL-1β y actúa como un marcador sensible de inflamación sistémica. A nivel molecular facilita la opsonización y activación del complemento, modulando tanto la respuesta inmunitaria innata como la adaptativa[61].

En oncología, una PCR elevada refleja una respuesta inflamatoria generalizada que puede estar vinculada a la secreción de citocinas por el tumor y su microambiente, así como a procesos infecciosos concomitantes[62]. Es por este motivo que ha emergido como un marcador pronóstico relevante en el cáncer colorrectal. Se ha descrito que el valor de PCR elevado en el preoperatorio puede ser un marcador pronóstico de supervivencia[63], algunos estudios han reportado diferencias de supervivencia a los 5 años de hasta el 30% entre aquellos pacientes que presentaban una PCR pre y postoperatoria baja respecto aquellos que la presentaban elevada[64]. Este patrón sugiere que la PCR no solo refleja la carga tumoral, sino también la magnitud de la

respuesta inflamatoria del huésped, lo cual puede promover un microambiente tumoral más agresivo.

El **índice plaqueta-linfocito** es un biomarcador hematológico de inflamación sistémica que ha demostrado relevancia pronóstica en oncología. Este marcador refleja la interacción entre la trombocitosis reactiva y la linfopenia relativa, lo que indica un estado inflamatorio sistémico y una respuesta inmunitaria deprimida, es por ello por lo que un IPL elevado se asocia con una peor supervivencia global, libre de enfermedad y una mayor tasa de recurrencia[65].

Se considera que el IPL se encuentra elevado cuando supera valores de 150-220, punto de corte variable según los estudios realizados. La determinación debe realizarse en el preoperatorio o antes de iniciar un tratamiento sistémico ya que el valor basal refleja el estado inflamatorio sistémico y la inmunidad del paciente en relación con la carga y el microambiente tumorales, sin factores de confusión inducidos por los diferentes tratamientos recibidos[66].

El **índice neutrófilo-linfocito** representa el cociente entre el número de neutrófilos, células mediadoras de inflamación y angiogénesis, y linfocitos, responsables de la respuesta inmunitaria antitumoral. Un valor elevado indica una activación proinflamatoria con supresión relativa de la inmunidad celular, situación que favorece el crecimiento tumoral y la evasión inmunológica.

Desde el punto de vista biológico, los neutrófilos promueven la progresión del tumor mediante la liberación de especies reactivas de oxígeno, metaloproteinasas y factores proangiogénicos como el VEGF. Al mismo tiempo, la linfopenia refleja una menor actividad de linfocitos T citotóxicos, esenciales en la vigilancia inmunológica contra células malignas[67].

En un metaanálisis de más de 40.000 pacientes con cáncer avanzado, se observó que un INL elevado se asociaba con una disminución significativa de la supervivencia global en múltiples tipos de tumores, incluido el CCR[68]. Asimismo, Chiang et al.[69] en una cohorte de más de 3.800 pacientes, demostraron que un INL >3 se asociaba con menor supervivencia libre de enfermedad, especialmente en pacientes con cáncer de colon.

Sin embargo, aunque numerosos estudios respaldan el poder predictivo del NLR[70,71], la mayoría corresponde a estudios observacionales retrospectivos que no controlan adecuadamente los factores de confusión. Además, los pocos estudios que

han homogeneizado la muestra mediante emparejamiento por puntuación de propensión[72,73] se han realizado con un número relativamente reducido de pacientes.

A diferencia del INL preoperatorio, que refleja el estado inflamatorio sistémico basal y ha sido ampliamente vinculado con la agresividad tumoral, diversos estudios recientes sugieren que el valor del INL tras la resección del tumor ofrece una estimación más precisa del riesgo de recurrencia y de la supervivencia global. Esta diferencia puede explicarse por la hipótesis de que la extirpación del tumor primario permite una recuperación parcial de la función inmunitaria, y que los niveles postoperatorios de INL representarían de forma más fiel el equilibrio inmuno/inflamatorio del paciente en ausencia del estímulo tumoral directo. Estudios como el de Guthrie[74] han demostrado que un INL elevado tras el tratamiento se asocia significativamente con peor evolución clínica, independientemente del estadio tumoral inicial, lo que respalda su utilidad como marcador de vigilancia a medio y largo plazo.

Estos datos han sido respaldados por un metaanálisis publicado en 2021 donde se analizaron 25 trabajos y se demostró que la elevación del INL postoperatorio, determinado al menos 7 días después de la cirugía, se asociaba con una peor supervivencia global y libre de enfermedad en tumores sólidos, incluido el CCR. La determinación del INL fue variable entre los estudios con un tiempo entre 1 y 6 meses tras la cirugía, con un punto de corte también variable entre 3 y 5[75]. Estos resultados sugieren que el INL determinado tras la resolución de la respuesta inflamatoria aguda postquirúrgica refleja mejor el estado inflamatorio sistémico persistente y la inmunidad del paciente, siendo útil para la estratificación del riesgo y la vigilancia oncológica en el seguimiento de pacientes con CCR.

Otro aspecto a estudio del INL es si la variabilidad de este parámetro a lo largo del tiempo puede influir en el pronóstico del CCR, es decir, si una normalización o una alteración del estado inflamatorio del paciente tras el tratamiento se puede traducir en cambios en el pronóstico. Un ejemplo de ello es la determinación del delta-INL, que es la diferencia entre el INL preoperatorio y el postoperatorio. Se ha observado que cuando esta diferencia es mayor a 0 las tasas de supervivencia global son mayores que en los que el delta-INL es menor a 0[76].

Los resultados anteriormente expuestos respaldan la hipótesis de que existen diversos parámetros analíticos, de fácil determinación, que pueden resultar útiles para estratificar el pronóstico de los pacientes con diagnóstico de CCR. Entre ellos destacan

la PCR, el IPL y, especialmente, el INL. Este último ha demostrado, de forma consistente en la literatura científica, ser el más útil en este contexto.

1.4. Complicaciones postoperatorias

La aparición de complicaciones tras la cirugía del CCR es un evento relativamente frecuente, ya sean complicaciones potencialmente quirúrgicas como la dehiscencia de anastomosis, complicaciones infecciosas o hemorrágicas o complicaciones médicas como eventos cardiovasculares, tromboembólicos y/o nefrológicos, entre otros.

La presencia de complicaciones postoperatorias se asocia con mayor riesgo de recurrencia tumoral y menor supervivencia global y específica, siendo este efecto más pronunciado en complicaciones graves. Particularmente, las complicaciones infecciosas se han identificado como factor independiente de peor pronóstico, incrementando el riesgo de recaída y la mortalidad a largo plazo[77].

Se cree que esta relación puede ser debida a la activación de respuesta inflamatoria sistémica, inmunosupresión transitoria y/o retraso en el inicio de los tratamientos adyuvantes, lo que puede favorecer la progresión tumoral y la diseminación micrometastásica. Algunos estudios sugieren que, si se logra evitar un retraso significativo en la administración de tratamiento adyuvante, el impacto negativo de las complicaciones postoperatorias podría atenuarse[78].

Con el propósito de estandarizar la valoración de la gravedad de las complicaciones postoperatorias, se han desarrollado y validado diversas escalas objetivas de estratificación, las cuales permiten unificar criterios diagnósticos y terapéuticos entre distintos especialistas, facilitando así la comparación interinstitucional e interdisciplinaria de resultados clínicos.

La clasificación de Clavien-Dindo es un sistema estandarizado utilizado internacionalmente para categorizar las complicaciones postoperatorias en función de su gravedad. Fue inicialmente propuesta en 1992 y posteriormente modificada y validada en 2004, con el objetivo de proporcionar una herramienta objetiva, reproducible y clínicamente relevante que permitiera la comparación de resultados quirúrgicos entre diferentes instituciones y estudios[79].

A diferencia de sistemas anteriores, la clasificación de Clavien-Dindo no se basa en juicios subjetivos del cirujano, sino en el tipo de intervención requerida para tratar la complicación, siendo así aplicable de forma estandarizada en diferentes contextos quirúrgicos.

La clasificación se subdivide en los diferentes grados:

- **Grado 0:** Ausencia de complicaciones
- **Grado I:** Cualquier desviación del curso postoperatorio normal sin necesidad de tratamiento farmacológico, quirúrgico, endoscópico ni radiológico. Se permite el uso de medicamentos como antieméticos, antipiréticos, analgésicos, diuréticos, electrolitos y fisioterapia. Incluye heridas quirúrgicas que requieren solo apertura sin anestesia.
- **Grado II:** Complicaciones que requieren tratamiento farmacológico con fármacos distintos a los permitidos para el grado I. Incluye transfusiones sanguíneas y nutrición parenteral total.
- **Grado III:** Complicaciones que requieren intervención quirúrgica, endoscópica o radiológica.
    - **Grado IIIa**: Intervención sin anestesia general.
    - **Grado IIIb**: Intervención bajo anestesia general.
- **Grado IV:** Complicaciones que ponen en peligro la vida del paciente, que requieren manejo en unidad de cuidados intensivos (UCI).
    - **Grado IVa**: Disfunción de un solo órgano.
    - **Grado IVb**: Disfunción multiorgánica.
- **Grado V:** Muerte del paciente.

Si bien la clasificación de Clavien-Dindo ha supuesto un avance significativo en la estandarización de la evaluación de las complicaciones postoperatorias, su principal limitación radica en que solo considera la complicación de mayor gravedad sufrida por el paciente, sin tener en cuenta la morbilidad acumulativa cuando existen múltiples eventos adversos. Para superar esta limitación, Slankamenac et al. propusieron en 2013 el *Comprehensive Complication Index* (CCI), una herramienta cuantitativa derivada directamente de la clasificación de Clavien-Dindo[80].

El CCI permite calcular un índice continuo entre 0 (sin complicaciones) y 100 (muerte del paciente), que refleja con precisión la carga total de morbilidad postoperatoria experimentada por un individuo. Este índice se basa en un modelo

matemático que pondera todas las complicaciones sufridas por el paciente según su grado en la escala de Clavien-Dindo, integrándolas en una sola puntuación. De este modo, el CCI representa de forma más sensible y exacta el impacto global de las complicaciones en el resultado quirúrgico.

Existe una fórmula para realizar el cálculo, pero en la práctica el cálculo se realiza frecuentemente utilizando herramientas electrónicas validadas, como la calculadora disponible en https://www.assessurgery.com.

La siguiente tabla presenta ejemplos ilustrativos de posibles complicaciones postoperatorias, categorizadas según la puntuación obtenida en el CCI y su correlación con los distintos grados de la clasificación de Clavien-Dindo:

CCI	Clavien-Dindo	Gravedad	Ejemplo
0	0	Sin complicaciones	-
1-20	I-II	Leves	Náuseas, Infección de herida
21-40	II-IIIa	Moderadas	Colección postquirúrgica, Neumonía
41-60	IIIb	Graves	Reintervención quirúrgica
61-99	IVa-IVb	Muy graves	Fracaso multiorgánico, UCI
100	V	Muerte	-

Como ventajas del CCI se puede mencionar que captura la carga acumulativa de morbilidad, incluso en presencia de múltiples complicaciones menores, que permite comparaciones más precisas entre series de pacientes y que facilita el análisis estadístico al ser una variable contínua.

El uso combinado del sistema de Clavien-Dindo y del CCI proporciona una visión integral del perfil de seguridad de un procedimiento quirúrgico, permitiendo tanto la identificación de complicaciones individuales significativas como la cuantificación global del impacto sobre la salud del paciente.

Considerando las múltiples repercusiones que conllevan las complicaciones postoperatorias en la cirugía del CCR tanto a corto plazo —como el incremento de la morbimortalidad, la prolongación de la estancia hospitalaria y el aumento de los costes sanitarios— como a largo plazo —particularmente en términos de un peor pronóstico oncológico—, uno de los principales objetivos en la práctica quirúrgica ha sido, durante años, la detección precoz de dichas complicaciones. Esta estrategia busca minimizar

las consecuencias derivadas de un diagnóstico tardío, optimizando así la evolución clínica del paciente y su supervivencia a largo plazo.

Una herramienta que ha demostrado ser de gran utilidad en la detección precoz de complicaciones en el postoperatorio del CCR es la PCR[81]. Se considera que una elevación de la PCR en el postoperatorio puede revelar la futura aparición de una complicación postoperatoria, siendo este parámetro la primera manifestación de un estado inflamatorio sistémico. Clásicamente el estudio principal ha sido para predecir la aparición de dehiscencia de anastomosis en el postoperatorio[82], con especial interés en qué día realizar la determinación y cuál es el valor a partir del que se debe sospechar la presencia de dehiscencia de anastomosis. En términos generales se acepta que la determinación el tercer o cuarto día[83] son los que presentan mayor sensibilidad y especificidad y que se debe sospechar dehiscencia de anastomosis en valores de PCR>130mg/L[84].

Menos evidencia hay sobre impacto del global de complicaciones postoperatorias sobre la PCR y, mayoritariamente se ha hecho clasificando las complicaciones según la clasificación de Clavien-Dindo[85]. Valores de PCR por encima de 150mg/L en el tercer o cuarto día postoperatorio se relacionaron con un Clavien-Dindo mayor de 3, según McSorley[86].

Aunque son escasos los estudios que han evaluado la relación entre la PCR y el CCI en cirugía colorrectal, Yong et al. lo utilizaron para cuantificar la morbilidad postoperatoria y propusieron que una PCR inferior a 64,7 mg/L permite un alta hospitalaria segura, con bajo riesgo de complicaciones postoperatorias[87].

La PCR ha mostrado ser el parámetro analítico por excelencia para la detección de complicaciones postoperatorias. No obstante, otros biomarcadores biológicos pueden ser de utilidad para ello, como es el caso del INL. Se ha estudiado ampliamente si la elevación de este marcador en el preoperatorio podría ser predictor de complicaciones postoperatorias, confirmando que se relaciona con las complicaciones infecciosas[88] y la dehiscencia de anastomosis, en este caso se estableció, en una serie de población de edad elevada, un punto de corte de INL preoperatorio >2,66[89].

Se ha demostrado también la utilidad de la monitorización del INL en el postoperatorio: en el primer día postoperatorio se ha descrito que un INL>9,3 se asocia con una mayor incidencia de complicaciones postoperatorias[90], mientras que un

INL<5,26 el tercer día postoperatorio presenta un alto valor predictivo negativo para descartar complicaciones postoperatorias[91].

Aunque los biomarcadores inflamatorios sistémicos han demostrado un valor potencial tanto en la predicción de complicaciones postoperatorias como en la estimación del pronóstico oncológico, la calidad metodológica de los estudios disponibles sigue siendo una limitación importante. Muchos de los trabajos publicados son de carácter retrospectivo, con poblaciones heterogéneas, sin control adecuado de los factores de confusión y con puntos de corte variables entre estudios, lo que dificulta su aplicación en la práctica clínica.

Además, muchos estudios no han abordado de forma simultánea los dos aspectos más relevantes desde el punto de vista clínico: la predicción de complicaciones postoperatorias (que pueden influir negativamente en la recuperación, la posibilidad de recibir tratamiento adyuvante y la calidad de vida del paciente) y la estimación del pronóstico a largo plazo (supervivencia global y libre de enfermedad).

Como ya se ha mencionado previamente, las complicaciones postoperatorias en pacientes intervenidos por CCR no solo representan un aumento en la morbimortalidad inmediata, sino que han sido consistentemente asociadas con un impacto negativo en el pronóstico oncológico a medio y largo plazo[92]. Diversos estudios han evidenciado que la presencia de complicaciones graves, en especial las infecciosas como la dehiscencia anastomótica o la sepsis abdominal, se correlaciona con una mayor tasa de recurrencia tumoral y una menor supervivencia global. Esta asociación ha sido atribuida, en parte, a la activación de un estado proinflamatorio sistémico en el postoperatorio que podría favorecer la diseminación tumoral residual o la creación de un microambiente prooncogénico[93].

Sin embargo, hallazgos más recientes, como los presentados por el grupo RectoLeak[94], cuestionan esta relación directa, sugiriendo que, gracias a los avances en el diagnóstico precoz y la optimización de las estrategias terapéuticas, la aparición de complicaciones postoperatorias —incluida la dehiscencia de anastomosis— no necesariamente se traduce en un peor pronóstico oncológico. Esta discrepancia entre estudios podría deberse a diferencias en el tiempo de intervención, la experiencia quirúrgica, los protocolos de seguimiento y el acceso a recursos asistenciales.

En cualquier caso, se mantiene la hipótesis de que marcadores inflamatorios como la PCR podrían desempeñar un papel crucial tanto en la detección temprana de complicaciones como en su manejo oportuno, contribuyendo así indirectamente a preservar el pronóstico a largo plazo. Además, la prolongación del ingreso hospitalario, la demora en la instauración de tratamientos adyuvantes y el deterioro funcional del paciente tras una complicación severa siguen representando factores clave que condicionan la evolución clínica.

Por tanto, la prevención, detección precoz y el manejo adecuado de las complicaciones postoperatorias no solo son fundamentales para la recuperación inmediata, sino que también constituyen un pilar esencial en el control oncológico integral del paciente.

2. BIBLIOGRAFÍA

1) International Agency for Research on Cancer. Cancer Tomorrow [Internet]. Lyon: International Agency for Research on Cancer; 2024 [citado 2025 May 17]. Disponible en: https://gco.iarc.fr/tomorrow
2) Sociedad Española de Oncología Médica, Red Española de Registros de Cáncer. Las cifras del cáncer en España 2024 [Internet]. Madrid: Sociedad Española de Oncología Médica; 2024 [citado 2025 May 17]. Disponible en: https://www.seom.org/images/LAS*CIFRAS*2024.pdf
3) Marcellinaro R, Spoletini D, Grieco M, Avella P, Cappuccio M, Troiano R, et al. Colorectal Cancer: Current Updates and Future Perspectives. J Clin Med. 2023;13(1):40. doi:10.3390/jcm13010040
4) Matsuda T, Fujimoto A, Igarashi Y. Colorectal Cancer: Epidemiology, Risk Factors, and Public Health Strategies. Digestion. 2025;106(2):91-99. doi:10.1159/000543921
5) Argilés G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(10):1291-305. doi:10.1016/j.annonc.2020.06.022
6) Davis DM, Marcet JE, Frattini JC, Prather AD, Mateka JJ, Nfonsam VN. Is it time to lower the recommended screening age for colorectal cancer? J Am Coll Surg. 2011;213(3):352-61. doi:10.1016/j.jamcollsurg.2011.04.033
7) Hansen IO, Jess P. Possible better long-term survival in left versus right-sided colon cancer - a systematic review. Dan Med J. 2012;59(6):A4444.
8) Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044-58. doi:10.1053/j.gastro.2010.01.054
9) Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679-87. doi:10.1093/jnci/dji375
10) Mattar MC, Lough D, Pishvaian MJ, Charabaty A. Current management of inflammatory bowel disease and colorectal cancer. Gastrointest Cancer Res. 2011;4(2):53-61.
11) Keller DS, Windsor A, Cohen R, Chand M. Colorectal cancer in inflammatory bowel disease: review of the evidence. Tech Coloproctol. 2019;23(1):3-13. doi:10.1007/s10151-019-1926-2

12) Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91(4):854-62. doi:10.1002/1097-0142(20010215)91:4<854::aid-cncr1073>3.0.co;2-z
13) Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the World Cancer Research Fund-American Institute for Cancer Research Continuous Update Project. Ann Oncol. 2017;28(8):1788-802. doi:10.1093/annonc/mdx171
14) Botteri E, Borroni E, Sloan EK, Bagnardi V, Bosetti C, Peveri G, et al. Smoking and colorectal cancer risk, overall and by molecular subtypes: a meta-analysis. Am J Gastroenterol. 2020;115(12):1940-9. doi:10.14309/ajg.0000000000000803
15) Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut. 2021;70(12):2330-6. doi:10.1136/gutjnl-2020-323450
16) Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112(3):580-93. doi:10.1038/bjc.2014.579
17) Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. J Clin Oncol. 2011;29(28):3775-82. doi:10.1200/JCO.2011.35.7566
18) Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713–32. https://doi.org/10.1038/s41575-019-0189-8.
19) Rentsch M, Schiergens T, Khandoga A, Werner J. Surgery for colorectal cancer – trends, developments, and future perspectives. Visc Med. 2016;32(3):184–91. https://doi.org/10.1159/000446490.
20) Vogel JD, Felder SI, Bhama AR, Hawkins AT, Langenfeld SJ, Shaffer VO, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of colon cancer. Dis Colon Rectum. 2022;65(2):148–77. https://doi.org/10.1097/DCR.0000000000002323.
21) Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. JAMA. 2021;325(7):669–85. https://doi.org/10.1001/jama.2021.0106.
22) Schrag D, Shi Q, Weiser MR, Gollub MJ, Saltz LB, Musher BL, et al. Preoperative treatment of locally advanced rectal cancer. N Engl J Med. 2023;389(4):322–34. https://doi.org/10.1056/NEJMoa2303269.

23) Wegner RE, Abel S, Monga D, Raj M, Finley G, Nosik S, et al. Utilization of adjuvant radiotherapy for resected colon cancer and its effect on outcome. Ann Surg Oncol. 2020;27(3):825–32. https://doi.org/10.1245/s10434-019-08042-y.
24) Van den Berg I, Coebergh van den Braak RRJ, Van Vugt JLA, et al. Actual survival after resection of primary colorectal cancer: results from a prospective multicenter study. World J Surg Oncol. 2021;19(1):96. https://doi.org/10.1186/s12957-021-02207-4.
25) Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023;73(3):233–54. https://doi.org/10.3322/caac.21772.
26) Lea D, Håland S, Hagland HR, Søreide K. Accuracy of TNM staging in colorectal cancer: a review of current culprits, the modern role of morphology and stepping-stones for improvements in the molecular era. Scand J Gastroenterol. 2014;49(10):1153–63. https://doi.org/10.3109/00365521.2014.950692.
27) Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. JAMA Oncol. 2017;3(2):211–19. https://doi.org/10.1001/jamaoncol.2016.4227.
28) Gholamalizadeh H, Zafari N, Velayati M, Fiuji H, Maftooh M, Ghorbani E, et al. Prognostic value of primary tumor location in colorectal cancer: an updated meta-analysis. Clin Exp Med. 2023;23(8):4369–83. https://doi.org/10.1007/s10238-023-01120-2.
29) Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst. 2015;107(3):dju427. https://doi.org/10.1093/jnci/dju427
30) Yamauchi M, Lochhead P, Morikawa T, Huttenhower C, Chan AT, Giovannucci E, et al. Colorectal cancer: a tale of two sides or a continuum? Gut. 2012;61(6):794–7. https://doi.org/10.1136/gutjnl-2012-302014.
31) Yuan H, Dong Q, Zheng B, Hu X, Xu JB, Tu S. Lymphovascular invasion is a high risk factor for stage I/II colorectal cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(28):46565–79. https://doi.org/10.18632/oncotarget.15425.
32) Wang X, Cao Y, Ding M, Liu J, Zuo X, Li H, et al. Oncological and prognostic impact of lymphovascular invasion in colorectal cancer patients. Int J Med Sci. 2021;18(7):1721–9. https://doi.org/10.7150/ijms.53555.
33) Betge J, Pollheimer MJ, Lindtner RA, Kornprat P, Schlemmer A, Rehak P, et al. Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting. Cancer. 2012;118(3):628–38. https://doi.org/10.1002/cncr.26310.

34) Knijn N, Mogk SC, Teerenstra S, Simmer F, Nagtegaal ID. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. Am J Surg Pathol. 2016;40(1):103–12. https://doi.org/10.1097/PAS.0000000000000518.
35) Yang Y, Huang X, Sun J, Gao P, Song Y, Chen X, et al. Prognostic value of perineural invasion in colorectal cancer: a meta-analysis. J Gastrointest Surg. 2015;19(6):1113–22. https://doi.org/10.1007/s11605-015-2761-z.
36) Lai YH, Wu LC, Li PS, Wu WH, Yang SB, Xia P, et al. Tumour budding is a reproducible index for risk stratification of patients with stage II colon cancer. Colorectal Dis. 2014;16(4):259–64. https://doi.org/10.1111/codi.12454.
37) Chen K, Collins G, Wang H, Toh JWT. Pathological features and prognostication in colorectal cancer. Curr Oncol. 2021;28(6):5356 83. https://doi.org/10.3390/curroncol28060447.
38) Barresi V, Reggiani Bonetti L, Ieni A, Caruso RA, Tuccari G. Histological grading in colorectal cancer: new insights and perspectives. Histol Histopathol. 2015;30(9):1059–67. https://doi.org/10.14670/HH-11-633.
39) Chen D, Huang JF, Liu K, Zhang LQ, Yang Z, Chuai ZR, et al. BRAFV600E mutation and its association with clinicopathological features of colorectal cancer: a systematic review and meta-analysis. PLoS One. 2014;9:e90607. https://doi.org/10.1371/journal.pone.0090607
40) Pesola, G., Epistolio, S., Cefalì, M., Trevisi, E., De Dosso, S., & Frattini, M. (2024). Neo-RAS Wild Type or RAS Conversion in Metastatic Colorectal Cancer: A Comprehensive Narrative Review. Cancers, 16(23), 3923. https://doi.org/10.3390/cancers16233923
41) Frăsânie VA, Marinca MV, Alexa-Stratulat T, Gafton B, Păduraru M, Adavidoaiei AM, et al. KRAS, NRAS, BRAF, HER2 and microsatellite instability in metastatic colorectal cancer: practical implications for the clinician. Radiol Oncol. 2019;53(3):265–74. https://doi.org/10.2478/raon-2019-0033.
42) Porru M, Pompili L, Caruso C, Biroccio A, Leonetti C. Targeting KRAS in metastatic colorectal cancer: current strategies and emerging opportunities. J Exp Clin Cancer Res. 2018;37:57. https://doi.org/10.1186/s13046-018-0719-1.
43) Wanebo HJ, Rao B, Pinsky CM, Hoffman RG, Stearns M, Schwartz MK, et al. Preoperative carcinoembryonic antigen level as a prognostic indicator in colorectal cancer. N Engl J Med. 1978;299(9):448–51. https://doi.org/10.1056/NEJM197808312990904.
44) Harrison LE, Guillem JG, Paty P, Cohen AM. Preoperative carcinoembryonic antigen predicts outcomes in node-negative colon cancer patients: a multivariate

analysis of 572 patients. J Am Coll Surg. 1997;185(1):55–9. https://doi.org/10.1016/s1072-7515(97)00012-4.

45) Thirunavukarasu P, Talati C, Munjal S, Attwood K, Edge SB, Francescutti V. Effect of incorporation of pretreatment serum carcinoembryonic antigen levels into AJCC staging for colon cancer on 5-year survival. JAMA Surg. 2015;150(8):747–55. https://doi.org/10.1001/jamasurg.2015.0871.

46) Ozawa H, Kotake K, Hosaka M, Hirata A, Nakagawa Y, Fujita S, et al. Incorporation of serum carcinoembryonic antigen levels into the prognostic grouping system of colon cancer. Int J Colorectal Dis. 2017;32(6):821–9. https://doi.org/10.1007/s00384-017-2772-1.

47) Lakemeyer L, Sander S, Wittau M, Henne-Bruns D, Kornmann M, Lemke J. Diagnostic and prognostic value of CEA and CA19-9 in colorectal cancer. Dis. 2021;9(1):21. https://doi.org/10.3390/diseases9010021.

48) Lee JO, Kim M, Lee JH, Kim Y, Lim HK, Kwon YH, et al. Carbohydrate antigen 19-9 plus carcinoembryonic antigen for prognosis in colorectal cancer: an observational study. Colorectal Dis. 2023;25(2):272–81. https://doi.org/10.1111/codi.16372.

49) Gefen R, Emile SH, Horesh N, Garoufalia Z, Wexner SD. Age-related variations in colon and rectal cancer: an analysis of the national cancer database. Surgery. 2023;174(6):1315–22. https://doi.org/10.1016/j.surg.2023.08.007.

50) Majek O, Gondos A, Jansen L, Emrich K, Holleczek B, Katalinic A, et al. Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. PLoS One. 2013;8(7):e68077. https://doi.org/10.1371/journal.pone.0068077.

51) Limam M, Matthes KL, Pestoni G, Michalopoulou E, Held L, Dehler S, et al. Are there sex differences among colorectal cancer patients in treatment and survival? A Swiss cohort study. J Cancer Res Clin Oncol. 2021;147(5):1407–19. https://doi.org/10.1007/s00432-021-03557-y.

52) Iversen LH, Nørgaard M, Jacobsen J, Laurberg S, Sørensen HT. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006: a population-based cohort study. Dis Colon Rectum. 2009;52(1):71–8. https://doi.org/10.1007/DCR.0b013e3181974384.

53) Erichsen R, Horváth-Puhó E, Iversen LH, Lash TL, Sørensen HT. Does comorbidity interact with colorectal cancer to increase mortality? A nationwide population-based cohort study. Br J Cancer. 2013;109(7):2005–13. https://doi.org/10.1038/bjc.2013.541.

54) Boakye D, Günther K, Niedermaier T, Haug U, Ahrens W, Nagrani R. Associations between comorbidities and advanced stage diagnosis of lung, breast, colorectal, and prostate cancer: a systematic review and meta-analysis. Cancer Epidemiol. 2021;75:102054. https://doi.org/10.1016/j.canep.2021.102054.

55) Ommundsen N, Wyller TB, Nesbakken A, Jordhøy MS, Bakka A, Skovlund E, et al. Frailty is an independent predictor of survival in older patients with colorectal cancer. Oncologist. 2014;19(12):1268–75. https://doi.org/10.1634/theoncologist.2014-0237.

56) Jiang W, Yu H, Liu Y, Xun F, Ma Z, Yang J, et al. Evaluation and application of frailty index in colorectal cancer: a comprehensive review. Am Surg. 2024;90(6):1630–7. https://doi.org/10.1177/00031348241227191.

57) Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357(9255):539–45. https://doi.org/10.1016/S0140-6736(00)04046-0.

58) Klaunig JE, Kamendulis LM, Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. Toxicol Pathol. 2010;38(1):96–109. https://doi.org/10.1177/0192623309356453.

59) Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436–44. https://doi.org/10.1038/nature07205.

60) Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149–63. https://doi.org/10.2217/fon.09.136.

61) Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol.2001;38(2–3):189–97.https://doi.org/10.1016/s0161-5890(01)00042-6.

62) Køstner AH, Fuglestad AJ, Georgsen JB, Nielsen PS, Christensen KB, Zibrandtsen H, et al. Fueling the flames of colon cancer: does CRP play a direct pro-inflammatory role? Front Immunol. 2023;14:1170443. https://doi.org/10.3389/fimmu.2023.1170443.

63) Pathak S, Nunes QM, Daniels IR, Smart NJ. Is C-reactive protein useful in prognostication for colorectal cancer? A systematic review. Colorectal Dis. 2014;16(10):769–76. https://doi.org/10.1111/codi.12700.

64) Yamamoto M, Saito H, Uejima C, Tanio A, Takaya S, Sakamoto T, et al. Prognostic value of the combination of pre- and postoperative C-reactive protein in colorectal cancer patients. Surg Today. 2018;48(11):986–93. https://doi.org/10.1007/s00595-018-1689-9.

65) Tan D, Fu Y, Su Q, Wang H. Prognostic role of platelet-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(24):e3837. https://doi.org/10.1097/MD.0000000000003837.

66) You J, Zhu GQ, Xie L, Liu WY, Shi L, Wang OC, et al. Preoperative platelet to lymphocyte ratio is a valuable prognostic biomarker in patients with colorectal cancer. Oncotarget. 2016;7(18):25516–27. https://doi.org/10.18632/oncotarget.8334.

67) Chen ZY, Raghav K, Lieu CH, Jiang ZQ, Eng C, Vauthey JN, et al. Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer. 2015;112(6):1088–97. https://doi.org/10.1038/bjc.2015.61.

68) Li MX, Liu XM, Zhang XF, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer. 2014;134(10):2403–13. https://doi.org/10.1002/ijc.28536.

69) Chiang SF, Hung HY, Tang R, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis. 2012;27(10):1347–57. https://doi.org/10.1007/s00384-012-1459-x.

70) He X, Su A, Xu Y, et al. Prognostic role of lymphocyte-C-reactive protein ratio in colorectal cancer: a systematic review and meta-analysis. Front Oncol. 2022;12:905144. https://doi.org/10.3389/fonc.2022.905144.

71) Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev. 2017;58:1–13. https://doi.org/10.1016/j.ctrv.2017.05.005.

72) Balde AI, Fang S, He L, et al. Propensity score analysis of recurrence for neutrophil-to-lymphocyte ratio in colorectal cancer. J Surg Res. 2017;219:244–52. https://doi.org/10.1016/j.jss.2017.05.109.

73) Mazaki J, Katsumata K, Kasahara K, et al. Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: a propensity score analysis. BMC Cancer. 2020;20:922. https://doi.org/10.1186/s12885-020-07429-5.

74) Guthrie GJK, Roxburgh CSD, Farhan-Alanie OM, Horgan PG, McMillan DC. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. Br J Cancer. 2013;109(1):24–8. https://doi.org/10.1038/bjc.2013.330.

75) Wu M, Yang S, Feng X, Li C, Yu F, Dong J. Prognostic value of the postoperative neutrophil-lymphocyte ratio in solid tumors: a meta-analysis. PLoS One. 2021;16(4):e0250091. https://doi.org/10.1371/journal.pone.0250091.
76) Li Z, Zhao R, Cui Y, Zhou Y, Wu X. The dynamic change of neutrophil to lymphocyte ratio can predict clinical outcome in stage I–III colon cancer. Sci Rep. 2018;8(1):9453. https://doi.org/10.1038/s41598-018-27896-y.
77) Warps AK, Tollenaar RAEM, Tanis PJ, Dekker JWT; Dutch ColoRectal Audit. Postoperative complications after colorectal cancer surgery and the association with long-term survival. Eur J Surg Oncol. 2022;48(4):873–82. https://doi.org/10.1016/j.ejso.2021.10.035.
78) Fransgaard T, Thygesen LC, Gögenur I. The impact of postoperative complications and delay of adjuvant chemotherapy on oncological outcomes in patients with colorectal cancer. Colorectal Dis. 2021;23(5):1132–40. https://doi.org/10.1111/codi.15538.
79) 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(2):205–13. https://pubmed.ncbi.nlm.nih.gov/15273542.
80) Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index. Ann Surg. 2013;258(1):1–7. https://doi.org/10.1097/SLA.0b013e318296c732.
81) Alsaif SH, Rogers AC, Pua P, Casey PT, Aherne GG, Brannigan AE, et al. Preoperative C-reactive protein and other inflammatory markers as predictors of postoperative complications in patients with colorectal neoplasia. World J Surg Oncol. 2021;19(1):74. https://doi.org/10.1186/s12957-021-02142-4.
82) Yeung DE, Peterknecht E, Hajibandeh S, Hajibandeh S, Torrance AW. C-reactive protein can predict anastomotic leak in colorectal surgery: a systematic review and meta-analysis. Int J Colorectal Dis. 2021;36(6):1147–62. https://doi.org/10.1007/s00384-021-03854-5.
83) Singh PP, Zeng ISL, Srinivasa S, Lemanu DP, Connolly AB, Hill AG. Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. Br J Surg. 2014;101(4):339–46. https://doi.org/10.1002/bjs.9354.
84) Sala Hernandez A, Frasson M, García-Granero A, Hervás Marín D, Laiz Marro B, Alonso Pardo R, et al. Diagnostic accuracy of C-reactive protein, procalcitonin and neutrophils for the early detection of anastomotic leakage after colorectal resection: a multicentric, prospective study. Colorectal Dis. 2021;23(10):2723–30. https://doi.org/10.1111/codi.15845.

85) McSorley ST, Ramanathan ML, Horgan PG, McMillan DC. Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer. Int J Colorectal Dis. 2015;30(7):913–7. https://doi.org/10.1007/s00384-015-2229-3.

86) McSorley ST, Watt DG, Horgan PG, McMillan DC. Postoperative systemic inflammatory response, complication severity, and survival following surgery for colorectal cancer. Ann Surg Oncol. 2016;23(9):2832–40. https://doi.org/10.1245/s10434-016-5204-5.

87) Jin HY, Hong I, Bae JH, Lee CS, Han SR, Lee YS, et al. Predictive factors of high comprehensive complication index in colorectal cancer patients using enhanced recovery after surgery protocol: role as a safety net in early discharge. Ann Surg Treat Res. 2021;101(6):340–9. https://doi.org/10.4174/astr.2021.101.6.340.

88) Fuss C, Nowacki M, Knipper S, Eichelberg AC, Lenschow C, Kneist W, et al. Preoperative neutrophil-to-lymphocyte ratio is associated with postoperative infectious complications after colorectal cancer surgery. Int J Colorectal Dis. 2022;37(12):2619–26. https://doi.org/10.1007/s00384-022-04203-4.

89) Wang X, Li J, Yan Y, Song X, Du H, Li L, et al. The impact of elevated preoperative neutrophil-to-lymphocyte ratio on symptomatic anastomotic leakage in elderly colorectal cancer patients: a multicenter retrospective cohort study. World J Gastrointest Surg. 2024;16(2):438–51. https://doi.org/10.4240/wjgs.v16.i2.438.

90) Cook EJ, Walsh SR, Farooq N, Alberts JC, Justin TA, Keeling NJ. Post-operative neutrophil-lymphocyte ratio predicts complications following colorectal surgery. Int J Surg. 2007;5(1):27–30. https://doi.org/10.1016/j.ijsu.2006.05.013.

91) Dos Santos BDN, Beruti C, Azevedo J, Herrando I, Vieira P, Domingos H, et al. Using inflammatory parameters for safe and early discharge after minimally invasive colorectal surgery for colorectal cancer. Tech Coloproctol. 2025;29(1):97. https://doi.org/10.1007/s10151-025-03134-2.

92) Hain E, Maggiori L, Manceau G, Mongin C, Prost à la Denise J, Panis Y. Oncological impact of anastomotic leakage after laparoscopic mesorectal excision. Br J Surg. 2017;104(3):288–95. https://doi.org/10.1002/bjs.10332.

93) Ishizuka M, Shibuya N, Takagi K, Hachiya H, Tago K, Sato S, et al. Impact of anastomotic leakage on postoperative survival of patients with colorectal cancer: a meta-analysis using propensity score matching studies. Surg Oncol. 2021;37:101584. https://doi.org/10.1016/j.suronc.2021.101538.

94) Gerdin A, Park J, Häggström J, Segelman J, Matthiessen P, Lydrup ML, et al. Anastomotic leakage after resection for rectal cancer and recurrence-free

survival in relation to postoperative C-reactive protein levels. Int J Colorectal Dis. 2024;39(1):193. https://doi.org/10.1007/s00384-024-04766-w.

3. JUSTIFICACIÓN

Aunque los biomarcadores inflamatorios han sido objeto de múltiples investigaciones, su integración práctica como herramientas predictivas y pronósticas en el cáncer colorrectal aún presenta importantes vacíos. En particular, la PCR ha sido tradicionalmente asociada a la predicción de la dehiscencia anastomótica. Sin embargo, su relación con la morbilidad postoperatoria global no ha sido suficientemente explorada. Esta tesis aborda esa laguna mediante su análisis en relación con el Comprehensive Complication Index (CCI), una herramienta cuantitativa que permite medir de forma continua la carga total de complicaciones tras la cirugía.

Del mismo modo, aunque el INL ha sido propuesto como factor pronóstico en distintos tipos de cáncer, incluido el CCR, la mayoría de estudios existentes presentan importantes limitaciones metodológicas. La tesis profundiza en este campo mediante el análisis del INL basal como predictor independiente de supervivencia, controlando los principales factores de confusión clínicos mediante técnicas estadísticas avanzadas.

Se estudia también el valor del INL al año del diagnóstico, una vez finalizados los tratamientos perioperatorios, y su influencia en el pronóstico del cáncer colorrectal, hallazgo que consideramos relevante y novedoso en la literatura científica.

Finalmente, una de las contribuciones más destacada de esta investigación es el desarrollo de una escala pronóstica en CCR que, por primera vez, integra de forma explícita las complicaciones postoperatorias, medidas mediante el CCI, como variable clave. Esta propuesta representa un avance en la estratificación de riesgo, combinando marcadores preoperatorios y eventos clínicos tempranos para ofrecer un modelo más ajustado al comportamiento real de la enfermedad.

Por tanto, esta tesis se justifica por su carácter integrador e innovador, y por su potencial aplicabilidad clínica. Al proporcionar herramientas accesibles y validadas para estimar el riesgo quirúrgico y oncológico, contribuye a una medicina más personalizada y eficiente, centrada en la mejora de los resultados y la calidad de vida de los pacientes con cáncer colorrectal.

4. OBJETIVOS

En base a lo anteriormente expuesto, nos propusimos analizar:

1) El significado pronóstico de las complicaciones postoperatorias clasificadas según el Comprehensive Complication Index.

2) La utilidad diagnóstica del valor de la Proteína C Reactiva en el postoperatorio en relación con las complicaciones postoperatorias distintas de la dehiscencia anastomótica.

3) El valor pronóstico del marcado inflamatorio “Índice Neutrófilo-Linfocito” al diagnóstico del cáncer colorrectal en un análisis de propensión.

4) El significado pronóstico de los valores del índice Neutrófilo-Linfocito en el postoperatorio tardío (un año después de la cirugía) y los cambios evolutivos en sus valores pre y postoperatorios.

5. RESULTADOS

En esta tesis se expondrán cuatro estudios consecutivos de carácter descriptivo y observacional, llevados a cabo en pacientes intervenidos por cáncer colorrectal de forma programada por la Unidad de Coloproctología del servicio de Cirugía General y del Aparato Digestivo del Hospital Universitario de Gran Canaria Doctor Negrín entre 2015 y 2022.

La presentación de los artículos en este trabajo se realiza en el orden que ha sido considerado más adecuado para comprender la consecución de objetivos, no por fecha de publicación.

1) **Ortiz-López, D.**, Marchena-Gómez, J., Nogués-Ramía, E., Sosa-Quesada, Y., Arencibia-Pérez, B., Artiles-Armas, M., & Roque-Castellano, C. (2022). Utility of a new prognostic score based on the Comprehensive Complication Index (CCI®) in patients operated on for colorectal cancer (S-CRC-PC score). Surgical oncology, 42, 101780. https://doi.org/10.1016/j.suronc.2022.101780

2) **Ortiz-López, D.**, Marchena-Gómez, J., Sosa-Quesada, Y., Artiles-Armas, M., Nogués-Ramia, E. M., Arencibia-Pérez, B., Gil-García, J. M., & Roque-Castellano, C. (2025). Utility of C-reactive protein on the fourth postoperative day to detect complications beyond anastomotic dehiscence. International journal of colorectal disease, 40(1), 124. https://doi.org/10.1007/s00384-025-04912-y

3) **Ortiz López, D.**, Marchena Gómez, J., Nogués Ramia, E. M., Sosa Quesada, Y., Arencibia Pérez, B., Artiles Armas, M., Gil García, J., & Roque Castellano, C. (2024). Prognostic value of neutrophil-to-lymphocyte ratio at diagnosis in colorectal cancer: propensity score analysis. Revista espanola de enfermedades digestivas, 116(8), 408–415. https://doi.org/10.17235/reed.2024.10041/2023

4) **Ortiz-López, D.**, Marchena-Gómez, J., Sosa-Quesada, Y., Artiles-Armas, M., Arencibia-Pérez, B., Gil-García, J., Nogués-Ramía, E., & Roque-Castellano, C. (2025). Prognostic impact of persistent postoperative neutrophil-to-lymphocyte ratio elevation 1 year after colorectal cancer surgery. Updates in Surgery. https://doi.org/10.1007/s13304-025-02286-y

ARTICULO I

“Utility of a new prognostic score based on the Comprehensive Complication Index (CCI) in patients operated on for colorectal cancer (S-CRC-PC score)”

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Utility of a new prognostic score based on the Comprehensive Complication Index (CCI®) in patients operated on for colorectal cancer (S-CRC-PC score)

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ABSTRACT

Background: Postoperative complications after colorectal cancer surgery have been associated with poor long-term prognosis. The aim of the present study was to investigate the prognostic impact of postoperative complications after colorectal cancer surgery assessed by the Comprehensive Complication Index (CCI®) and designing a new prognostic score based on this index.

Methods: This observational longitudinal study included a series of 604 patients who underwent colorectal surgery for cancer. Demographic data, comorbidity measured by Charlson Index, tumor characteristics, surgical data and postoperative complications were recorded as predictors. Univariate and multivariate analysis were performed and long-term survival was the output variable. Based on Hazard Ratios obtained on multivariate analysis, a new score, S-CRC-PC, was created for predicting long-term survival.

Results: Two-hundred and twelve (35.1%) patients developed some postoperative complication. The mean CCI was 11.6 (±19.19). Mild complications (CCI <26.2) were detected in 95 (15.7%) patients. Moderate complications (CCI 26.2–42.2) were detected in 64 (10.6%) patients. Severe complications (CCI >42.3) were detected in 53 patients (8.8%) patients. Mortality rate was 1.7%. In multivariate analysis, age ($p < 0.001$), Charlson score ($p = 0.014$), CCI ($p < 0.001$), and TNM stage ($p < 0.001$) were statistically significantly in relation to long-term survival rate. S-CRC-PC score was statistically associated with survival rate (HR: 1.34–95% CI: 1.27–1.41). Patients with S-CRC-PC values from 0 to 8 points (low risk), 8.1–16 points (medium risk), and scores above 16 points (high risk) had a cumulative survival rate at five-years of 98%, 83%, and 31% respectively.

Conclusions: Postoperative complications after colorectal cancer surgery assessed by CCI are an independent prognostic factor of survival rate. The S-CRC-PC score may be helpful in predicting long-term cancer outcomes.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide in both men and women. It is estimated that 52,980 deaths (28,520 men and 24,460 women) will be attributed to colorectal cancer in 2021 [1]. Although this mortality has been decreasing in recent years due to the latest diagnostic and therapeutic advances, this disease continues to be a major health problem. In fact, colorectal cancer is the second leading cause of cancer death in the United States for men and women combined. Overall, the 5-year survival rate for people with colorectal cancer, is around 65% [2].

Several factors related to the long-term survival of this neoplasm have been described.

Probably, tumor stage is the most relevant factor [3] together with other histopathological determinants such as microsatellite stability [4], tumor budding [5], lymphovascular invasion and/or perineural invasion [6], social determinants [7], tumor location [8], microenvironmental factors [9], and several new biomarkers [10–12].

Several reports have been published on the effect of some postoperative complications, predominantly anastomotic leak, as a predictive factor of diminished survival rate after curative resection for colorectal cancer [13].

However, only a few studies have linked the quantification of global postoperative complications with long-term survival in patients with

Abbreviations: CCI, Comprehensive Complication Index; CRC, Colorectal cancer.

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CRC. In most of them [14,15], the severity of postoperative complications was measured mainly with the Clavien-Dindo classification [16]. This grading system reports the most severe of all the complications that have occurred during the postoperative period. Another score, the Comprehensive Complication Index (CCI) [17], that provides a more sensitive endpoint for assessing postoperative complications [18], has been less documented as predictor for long-term survival [19,20].

The aim of this study was to analyze the possible relationship between postoperative complications after radical CRC resection, quantified according to CCI score, and long-term survival, adjusted for age, comorbidity and tumor stage. Also, we define a new prognostic index that includes postoperative complications in order to better understand the long-term prognosis of these patients.

2. Methods

2.1. Study design

An observational retrospective study from a prospective database was conducted on a cohort of 604 patients who underwent elective surgery for colorectal cancer between January 2015 and December 2019 in our institution. All patients, including stage IV, underwent surgery with curative intent. Exclusion criteria included patients with complicated CRC who required emergency surgery and those whose clinical records or follow-up was incomplete or not available. The number and characteristics of these excluded patients were not collected. The study was approved by the Ethics Committee of the hospital (Code 2020-279-1). All patients consented to participate in the study.

2.2. Management of the patient

A surgeon and an anesthesiologist pre-operatively evaluated all patients, and a complete anamnesis and physical examination were completed. The preoperative diagnosis of CRC was made by colonoscopy and biopsy in all the patients. The definitive diagnosis of CRC was made by postoperative histo-pathological examination according to the diagnostic criteria from the American Joint Committee on Cancer staging system (AJCC) (8th edition) [21]. All patients underwent preoperative thoraco-abdominal tomography and/or pelvic magnetic resonance imaging to determine the extent of the neoplasm. Laboratory tests, electrocardiograms, and additional tests were also performed based on each patient's underlying condition.

The day before surgery, anterograde colon mechanical preparation was implemented in addition to preoperative antibiotic prophylaxis before the surgical intervention. A single 2 g dose of intravenous Amoxicillin-clavulanic acid or 600 mg of Clindamycin plus 2 mg/kg of Gentamicin in allergic patients, were administered 30 min before surgery. All the surgical procedures were performed by a specialized surgeon and the anastomosis were accomplished using mechanical suture devices.

The data were gathered from a prospectively maintained database. The following variables were evaluated:

2.3. Patient characteristics

Age and sex were recorded. For purpose of the analysis, age was categorized in three groups: patients <65 years, patients between 65 and 75 years-old, and patients >75 years-old

2.4. Comorbidity

The Charlson Comorbidity Index was used to estimate the weights of comorbidities found in the sample. This index was calculated preoperatively for each patient. The score includes 19 medical conditions with assigned point values of 1, 2, 3, or 6, with totals ranging from 0 to 37 points [22]. Usually, 0 points represent the absence of comorbidity; low levels of comorbidity 1–2 points; moderate levels of comorbidity 3–4 points; and high levels of comorbidity are >4 points. In this study, Charlson score was not adjusted for age.

2.5. Tumor characteristics

Tumor location was categorized as colon cancer or rectum cancer. Tumor staging was performed in accordance with the 8th edition of the American Joint Committee on Cancer staging system (TNM) [23], and was graded as stages 0, I, II, III, and IV. Stage 0 corresponded to carcinomas "in situ", usually in the context of degenerated colorectal polyps.

2.6. Surgical data

Surgical procedure, surgical approach (open versus laparoscopy), postoperative complications, length of stay, and postoperative mortality were recorded.

2.7. Post-operative complications

They were graded using the CCI® [17]. The index is based on the complications grading by Clavien-Dindo Classification [16] and implements every occurred complication after an intervention. It was developed integrating in one single formula all recorded complications weighted by severity [17]. This score, that summarizes all postoperative complications, ranges from 0 (uneventful course) to 100 points (death), and it was analyzed categorized as follows [24]: no complications (Grade 0: 0 points), mild (Grade A: 1–26.1 points), moderate (Grade B: 26.2–42.2 points), and serious (Grade C: >42.3 points) complications. The CCI was calculated using the online calculator provided at https://www.assessurgery.com/about_cci-calculator/. Length of stay was defined as the number of days the patients spent in the hospital after the surgical procedure. Post-operative mortality was defined as either any death occurring within 90 days of surgery or any later death that was considered to be direct consequence of a postoperative complication.

2.8. Chemotherapy

Data was also collected on whether the patient received any adjuvant and/or neoadjuvant chemotherapy regimen. The decision to administer chemotherapy was made based on the Protocols of the multidisciplinary Colorectal Cancer Committee of the hospital. Patients with T3 or T4 rectal cancer and/or with lymph node involvement received neoadjuvant treatment with chemotherapy and radiotherapy. Patients with metastatic colon cancer, with potentially resectable liver and/or lung lesions, underwent neoadjuvant chemotherapy. For purpose of the survival analysis, the variable chemotherapy was dichotomized: patients who did not receive chemotherapy versus patients who received neo and/or adjuvant chemotherapy.

2.9. Outcomes

Long-term survival rate was defined as the period between the performance of the surgical procedure and death or the date of the last follow-up observation before the analysis, if the subject was still alive. Their respective statuses were monitored through their medical history or telephone contacts or their relatives' telephone numbers. Recurrence-free survival was defined as the time between the complete removal of the tumor and the date of recurrence confirmed by histology or radiology.

2.10. Statistical analysis

The data were analyzed using the statistical package SPSS 26.0 for Windows (IBM Corporation, Armonk, NY, USA). First, a descriptive

study of the sample was carried out. Categorical variables were expressed as frequencies and percentages. Continuous variables such as the mean and standard deviation (SD) when data followed a normal distribution or as median and interquartile range (IQR = 25–75th percentile) when distribution departed from normality were used. The survival curves were constructed using the Kaplan-Meier method.

Univariate and multivariate analysis were then performed. Survival rate after the surgical procedure was the output variable. The differences between the survival curves were tested by the log-rank test. The relative prognostic significance of the variables in predicting overall survival was assessed using multivariate Cox proportional hazards regression analysis. Hazard ratios were also calculated as association measurements using a Cox regression model. Statistical significance was defined as $p < 0.05$.

2.11. S-CRC-PC (Survival – colorectal cancer – postoperative complications) score

Based on the values of the hazard ratios obtained in Cox regression, simple points were assigned to each variable after multiplying the order number of each category of the variable in which the patient was included by the value of the hazard ratio. The definitive value of the S-CRC-PC score was the sum of all these values for every patient (Table 1).

Finally, the score S-CRC-PC was also divided into 3 categories: low, medium, and high risk of death during the follow-up. The cut-offs were based on the observed results of survival tables. A calculation of CCR-CCI score can be obtained free of charge at https://drive.google.com/file/d/1Z9qz1fJ-e6QQNGwJuDjncG2vk70D2zY_/view?usp=sharing (download is required).

3. Results

3.1. Patient characteristics

Out of the 604 patients, 373 (61.8%) were men and 231 (38.2%) were women (38.5%) ($p < 0.001$). Mean age was 68 years (±11.1) and median age was 70 years (IQR: 62.0–76.0), with 319 patients (52.8%) being older than 70 years.

3.2. Comorbidity

The median value of Charlson Index was 3.0 (IQR: 2.0–3.0). Charlson score was <4 (low comorbidity) in 284 (47.0%) patients, 3–4 (moderate comorbidity) in 244 (40.4%) patients, and >4 (high comorbidity) in 76 (12.6%). No one patient had zero comorbidity.

3.3. Tumor characteristics

Tumor location and TNM stages are shown in Table 2. The most frequent tumor location was the right side (33.6%). Regarding rectal location, the neoplasm was located in the rectum in 171 (28.3%) patients.

3.4. Surgical procedures

The procedures performed are displayed in Table 2. The laparoscopic approach was used in 349 (57.8%) cases. Thirteen (3.7%) patients initially submitted to laparoscopic surgery were reconverted to open surgery due to technical difficulties. The reestablishment of intestinal continuity by anastomosis was performed in 591 (97.8%) patients.

3.5. Postoperative complications

Two-hundred and twelve (35.1%) patients developed some postoperative complication, most of them mild complications (grade A). CCI mean was 11.6 (±19.19) and CCI median was 0.0 (IQR: 0.0–20.9). The most frequent surgical complication was prolonged adynamic ileus in 82 (13.6%) patients, requiring parenteral nutrition 49 of them. Forty-six (7.6%) patients presented gastrointestinal bleeding, most of them did not require treatment, with the bleeding stopping spontaneously. Thirty-one (5.2%) of 591 anastomosed patients had an anastomotic dehiscence, 26 of whom required reoperation. Twenty-one (3.5%) patients developed wound infection, and 15 (2.5%) patients a postoperative abdominal collection. Other postoperative surgical complications were complete wound dehiscence (9 cases), intestinal perforation (7 patients), mechanical intestinal obstruction (6 cases), hemoperitoneum (4 cases), gastric volvulus (1 case), acute mesenteric ischemia (1 case), and ureteral iatrogenic injury (3 cases).

3.6. Chemotherapy

No chemotherapy was administered in 328 (54.3%) patients and 276 (45.7%) received neo and/or adjuvant chemotherapy. Out of these, 99 (16.4%) patients received neoadjuvant therapy. Neo and adjuvant

Table 1
Calculation of the S-CRC-PC score. Low risk: 0–8 points, intermediate risk: 8.1–16 points, and high risk of death during the follow-up: >16 points.

Age		
<65 years-old = 1	x 2.2	= A
65-75 years-old = 2		
>75 years-old = 3		
CCI		
CCI 0 = 0	x 1.4	= B
CCI <26.2 = 1		
CCI 26.2–42.2 = 2		
CCI >42.3 = 3		
Charlson Comorbidity Score		
Charlson 0 = 0	x 1.4	= C
Charlson 1–2 = 1		
Charlson 3–4 = 2		
Charlson >4 = 3		
TNM stage:		
TNM Stage 0 = 0	x 2	= D
TNM Stage 1 = 1		
TNM Stage 2 = 2		
TNM Stage 3 = 3		
TNM Stage 4 = 4		
Total S-CRC-PC score		**=A+B+ C+D**

Table 2
Tumor characteristics and surgical procedures.

	Frequency (%)
Tumor location	
Right side	203 (33.6)
Transverse	36 (6.0)
Left side	56 (9.3)
Sigmoides	130 (21.5)
Rectum	171 (28.3)
Synchronous	8 (1.3)
Total	604 (100.0)
TNM stage	
0	56 (9.3)
1	110 (18.2)
2	216 (35.8)
3	183 (30.3)
4	39 (6.5)
Total	604 (100.0)
Surgical procedures	
Right colectomy	217 (35.9)
Left colectomy	57 (9.4)
Sigmoidectomy	123 (20.4)
Segmentary resection	20 (3.3)
Rectal anterior resection	168 (27.8)
Total colectomy	13 (2.2)
Abdominoperinal resection	6 (1.0)
Total	604 (100.0)

chemotherapy were both administered in 61 (10.1%) patients.

3.7. Length of stay

Median length of stay was 7 days (IQR: 5.0–11.0)

3.8. Postoperative mortality

Of the 604 patients, 10 (1.7%) patients died in the postoperative period (90 days). Seven of them as result of complications of the surgical intervention: anastomosis dehiscence (2 cases), pulmonary complications (3 cases), acute ischemia mesenteric (1 case), and catheter related sepsis (1 case). Two more patients died because of chemotherapy (one bone marrow aplasia and a massive pulmonary thromboembolism). The last patient died of unknown causes.

3.9. Long-term survival

The median length of follow-up was 3.5 years. By the end of the follow-up period, 114 (18.9%) patients had died, and 490 (81.1%) were still alive.

The cumulative survival at 1, 3 and 5 years were 94.5%, 86.8%, and 75.5%, respectively. Due to the high prevalence of censoring in this cohort, the median survival time could not be estimated. The mean estimated survival time was 64.6 months (5.4 years) (SE:0.97; 95%CI: 62.7–66.6). Out of the 114 patients who died during follow-up, 69 (60.5%) patients died due to tumor progression, and 45 (39.5%) patients died due to non-tumor-related causes.

Regarding tumor recurrence, 99 (16.4%) patients were diagnosed with neoplastic relapse during follow-up. The cumulative recurrence-free survival rate at 1, 3 and 5 years were 93.8%, 83.8%, and 81.5%. The mean estimated recurrence-free survival was 65.2 months (5.4 years) (SE:0.97; 95%CI: 63.3–67.1). The median could not also be estimated in this case.

3.10. Univariate and multivariate analysis

The relationship between the different predictor variables and the CCI grades (0, A, B, C, D) are shown in Table 3. Gender female ($p < 0.001$), rectum location ($p = 0.005$), open surgery ($p < 0.001$), and neoadjuvant chemotherapy ($p = 0.021$) presented significantly more postoperative complications.

The results of univariate and multivariate analysis related to survival time are shown in Table 4. CCI was related with both, global survival time ($p < 0.001$; HR: 1.02 – CI95%: 1.02–1.03), and recurrence-free survival rate ($p = 0.003$; HR: 1.02 – CI95%: 1.01–1.02).

The variable laparoscopic approach was not included in the multivariate analysis since this predictor could induce bias. The cases selected for laparoscopy were generally younger patients with less advanced disease. Note that there were no significant differences in survival between patients with colon cancer and rectal cancer ($p = 0.593$) (Fig. 1).

3.11. S-CRC-PC (Survival – colorectal cancer – postoperative complications) score

According to the obtained hazard ratio for each variable in multivariate analysis, the S-CRC-PC score was developed for every patient as is recorded in Table 1. S-CRC-PC score was statistically associated with survival rate (HR:1.34–95% CI: 1.27–1.41). Patients were 34% more likely to die during follow-up for each unit that the score increased in our series. The median value of the S-CRC-PC of the entire cohort was 11.2 (IQR: 9.4–14.0). Patients with S-CRC-PC values from 0 to 8 points were considered to have low risk (cumulative survival at five-years: 98%) while S-CRC-PC scores from 8.1 to 16 points were considered to have medium risk (cumulative survival at five years: 83%), and patients with S-CRC-PC scores above 16 points were considered to have high risk of death (cumulative survival at five years: 31%) during the follow-up (Fig. 2). Similar results were obtained with disease-free survival curves (Fig. 3).

Regarding the location of the neoplasm (colon vs. rectum), the S-CRC-PC score was also statistically significantly related to survival when differentiating between patients with colon cancer ($p < 0.001$) (Fig. 4) and rectal cancer ($p = 0.001$) (Fig. 5).

Table 3
Postoperative complications according to CCI. Grade 0: no complications; grade A: mild complications; grade B: moderate complications; grade C: severe complications. †Laparoscopic approach: 13 converted patients to open surgery were not included.

	Grade 0 (CCI = 0) n (%) 392 (64.9%)	Grade A (CCI <26.2) n (%) 95 (15.7%)	Grade B (CCI 26.2–42.2) n (%) 64 (10.6%)	Grade C (CCI >42.3) n (%) 53 (8.8%)	p
Age:					
<65 y.o.	131 (33.4)	23 (24.2)	17 (26.6)	19 (35.8)	0.227
65-75 y.o.	164 (41.8)	38 (40.0)	29 (45.3)	17 (32.1)	
>75 y.o.	97 (24.7)	34 (35.8)	18 (28.1)	17 (32.1)	
Gender:					
Men	226 (57.7)	52 (54.7)	50 (78.1)	45 (84.9)	<0.001
Women	166 (42.3)	43 (45.3)	14 (21.9)	8 (15.1)	
Charlson Score:					
1-2	189 (48.2)	44 (46.3)	33 (51.6)	18 (34.0)	0.564
3-4	153 (39.0)	39 (41.1)	24 (37.5)	28 (52.8)	
>4	50 (12.8)	12 (12.6)	7 (10.9)	7 (13.2)	
Tumor location:					
Colon	296 (75.5)	72 (75.8)	38 (59.4)	31 (58.5)	0.005
Rectum	96 (24.5)	23 (24.2)	26 (40.6)	22 (41.5)	
Laparoscopic approach†:					
No	135 (35.2)	52 (57.8)	29 (45.3)	26 (50.0)	<0.001
Yes	249 (64.8)	38 (42.2)	35 (54.7)	26 (50.0)	
Neoadjuvant Chemotherapy:					
No	336 (85.7)	82 (86.3)	46 (71.9)	41 (77.4)	0.021
Yes	56 (14.3)	13 (13.7)	18 (28.1)	12 (26.6)	
TNM stage:					
0	42 (10.7)	8 (8.4)	4 (6.3)	2 (3.8)	0.123
1	78 (19.9)	13 (13.7)	8 (12.5)	11 (20.8)	
2	132 (33.7)	44 (46.3)	20 (31.3)	20 (37.7)	
3	116 (29.6)	22 (23.2)	27 (42.2)	18 (34.0)	
4	24 (6.1)	8 (8.4)	5 (7.8)	2 (3.8)	

4. Discussion

The influence of postoperative complications on long-term prognosis in patients with colorectal carcinoma has been studied in the last two decades. Anastomotic dehiscence has perhaps been the most reported and studied complication. Its impact on long-term survival was initially questioned [25]. Nevertheless, a recent meta-analysis using propensity score matching studies [26], demonstrated a significantly decreased 5-year overall survival in patients with colorectal cancer who had anastomotic leakage compared with patients who did not have this surgical complication.

Regarding overall postoperative complications, Artiyan et al. [27] found that the presence of postoperative complications after CRC resection was associated with decreased long-term survival, independent of patient, disease, and treatment factors in a cohort of 12,075 patients. These authors related this negative impact on long-term outcome mainly with infectious complications. However, a quantification system for these complications was not reported. Other authors [14,15], using Clavien-Dindo classification, demonstrated that patients with overall postoperative complications after colorectal surgery have a poor oncologic long-term prognosis, with increasing effect with higher Clavien-Dindo score.

Our results also showed that high scores for the CCI were associated

Table 4
Univariate analysis and multivariate analysis (Cox Regression) adjusting CCI for the statistically significant predictors in univariate analysis. CCI: Comprehensive Complication Index; HR: Hazard ratio; CI 95%: Confidence Interval 95%. †Laparoscopic approach: 13 converted patients to open surgery were not included. ††Neo and/or adjuvant chemotherapy.

	N (%)	Univariate analysis		Adjusted CCI (multivariate analysis)	
		HR (95% CI)	p	HR (95% CI)	p
Age:					
<65 y.o.	190 (31.5)	2.07 (1.60–2.67)	<0.001	2.21 (1.72–2.84)	<0.001
65-75 y.o.	248 (41.1)				
>75 y.o.	166 (27.5)				
Gender:					
Men	373 (61.8)	1.11 (0.92–1.35)	0.284	–	–
Women	231 (38.2)				
Charlson Score:					
1-2	284 (47.0)	1.98 (1.54–2.54)	<0.001	1.43 (1.08–1.91)	0.014
3-4	244 (40.4)				
>4	76 (12.6)				
Tumor location:					
Colon	437 (72.4)	0.89 (0.59–1.36)	0.593	–	–
Rectum	167 (27.6)				
Laparoscopic approach†:					
No	242 (41.0)	0.46 (0.31–0.68)	<0.001	–	–
Yes	348 (59.0)				
Chemotherapy††:					
No	328 (54.3)	0.91 (0.63–1.32)	0.610	–	–
Yes	276 (45.7)				
TNM stage:					
0	56 (9.3)	1.85 (1.56–2.20)	<0.001	1.80 (1.48–2.19)	<0.001
1	110 (18.2)				
2	216 (35.8)				
3	183 (30.3)				
4	39 (6.4)				
CCI:					
0	392 (64.9)	1.42 (1.22–1.67)	<0.001	1.43 (1.22–1.68)	<0.001
<26.2	95 (15.7)				
26.2–42.2	64 (10.6)				
>42.2	53 (8.8)				

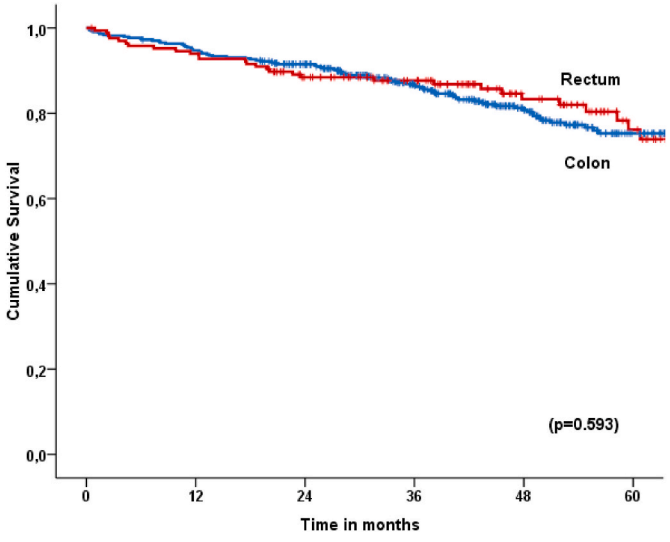

Fig. 1. Differences in cumulative survival between patients with colon cancer and rectum cancer (p = 0.593).

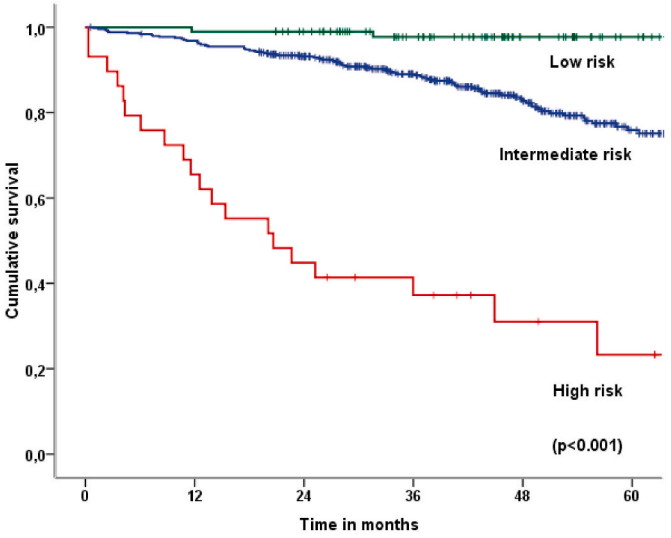

Fig. 2. Cumulative survival in months according to each category of the S-CRC-PC score (p < 0.001).

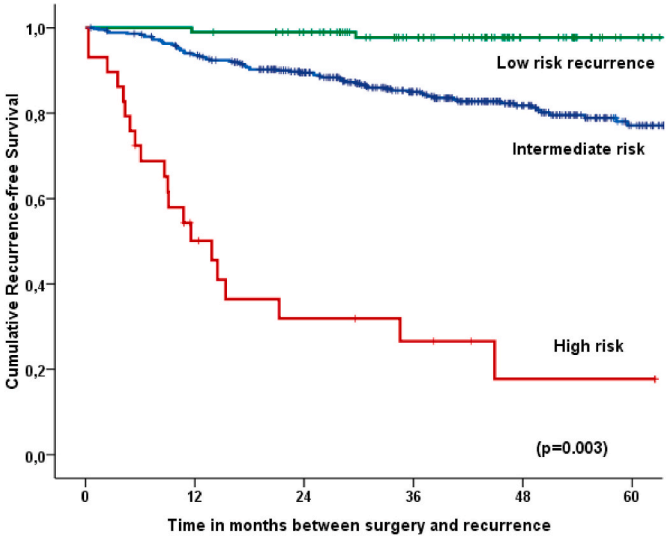

Fig. 3. Cumulative recurrence-free survival in months according to each category of the S-CRC-PC score (p = 0.003).

with a significant decrease in survival. After adjusting the CCI with other confounders, the increase from one grade to another higher grade (0, A, B, C) was associated with a 43% increase in the probability of dying during follow-up. These results are similar to those reported by Slankamenac [20] and Wang et al. [19], who observed that the score obtained from the CCI was inversely related to long-term survival.

It is worth noting that only few studies analyze the usefulness of CCI predicting overall survival after colorectal cancer surgery. We believe that CCI is more accurate than the Clavien-Dindo classification in appraising the severity of postoperative complications [28]. Clavien-Dindo score focuses only on the most serious complication, while the CCI integrates all postoperative complications that have occurred [29]. In fact, in the study of Slankamenac et al. [20] using both scores, they found that the presence of any complication or the use of the most severe complication only (grade ≥ IIIb) was not associated with readmission or overall survival. Instead, the CCI was a more sensitive and independent predictor of both outcomes, readmission and poorer long-term survival after surgery for CRC. However, Wang et al. [19], analyzing a greater number of patients concluded that both scores were

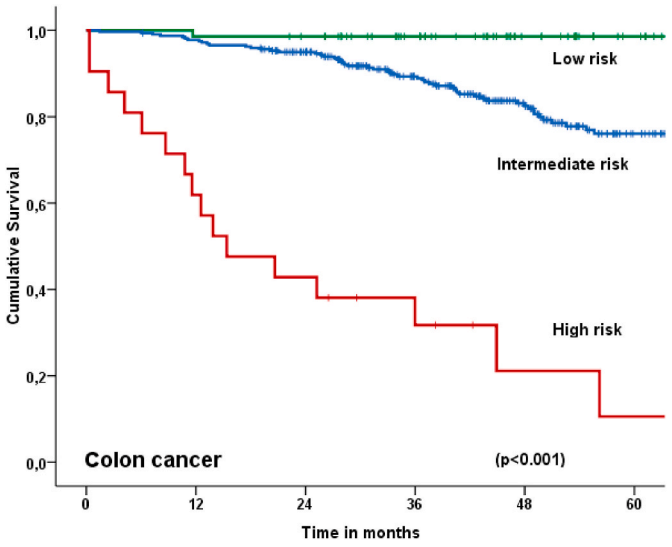

Fig. 4. Patients with colon cancer: cumulative survival in months according to each category of the S-CRC-PC score ($p < 0.001$).

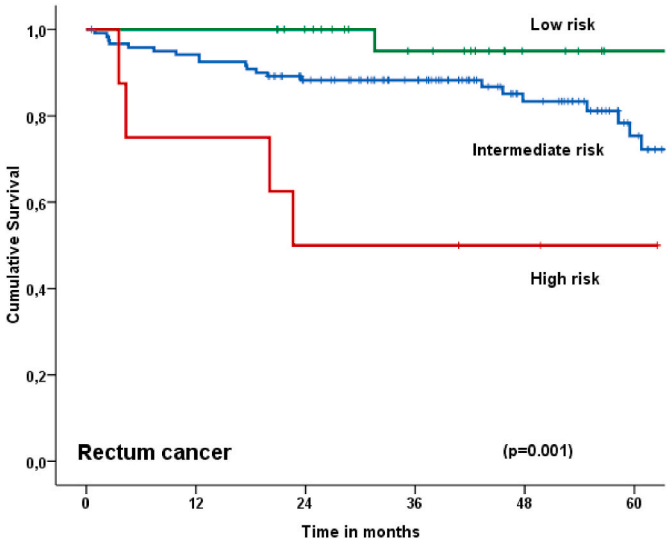

Fig. 5. Patients with rectum cancer: cumulative survival in months according to each category of the S-CRC-PC score ($p = 0.001$).

associated with long-term survival in elderly patients undergoing radical colorectal resection.

With regard to other tumor pathologies, it has been found that high CCI is a potent predictor of worse recurrence-free survival and cancer-specific survival after resection of colorectal metastasis [30]. Other report [31] concluded that negative oncological impact of postoperative complications after colorectal liver metastasis resection is determined by infective etiology rather than by CCI severity grading. Regarding gastric cancer surgery, a study [28] demonstrated that the complication severity graded by CCI reflects the difference of cancer-specific survival in gastric cancer patients with postoperative complications.

The association between postoperative complications and long-term survival has been related to a possible alteration in the baseline immune status of these patients. It has been postulated that an excessive postoperative inflammatory response may be followed by a dramatic paralysis of cell-mediated immunity in the surgical patient and an increased susceptibility to postoperative infectious complications [32]. Also, some authors believe that this process of cell-mediated immunity suppression may affect the immune response to the spreading of tumor cells, thereby contributing to an increased susceptibility of metastatic growth in oncological patients [33,34]. This could explain the observed reduction in long-term survival in these cancer patients [28,35], and our study supports these hypotheses: CCI was an independent risk factor for long-term survival in patients operated on for colorectal cancer. Saeki et al. [35] also found that the prognosis in patients who developed postoperative complications was worse in patients with less advanced neoplasms.

Catecholamines and prostaglandins have been recently implicated in these processes, and in directly promoting tumor angiogenesis and invasion. In an experimental study in rats reported by Goldfarb et al. [34], these authors concluded that treatments aimed at perioperative enhancement of cell-mediated immunity and simultaneous inhibition of excessive catecholamine and prostaglandin responses (pharmacological blockade with propranolol and etodolac), could be successful in limiting postoperative immunosuppression and metastatic progression, more so than each treatment alone.

On the other hand, achieving an adequate perioperative nutritional status is considered essential in order to prevent major postoperative complications and reducing surgical stress, especially for high-risk patients [36].

The impact of timing of adjuvant chemotherapy on survival in colorectal cancer patients has been also studied. Previous studies have shown that severe postoperative complications are associated with omission, delay, or discontinuation of adjuvant chemotherapy [14]. It has been demonstrated that delayed adjuvant chemotherapy after 8 weeks seems to be significantly associated with worse overall survival [37]. This circumstance could also explain the worse prognosis of colorectal cancer patients who have had postoperative complications. However, the relationship between complications, delayed chemotherapy and worsening survival could not be assessed in our study.

Other independent mortality risk factors observed in our series were age, comorbidity, and tumor stage. It has been well documented that elderly patients with colorectal cancer have worse prognosis than younger patients [38]. The underlying reasons for this disparity could be related to several factors such as frailty [39], or worse overall physical condition, which may affect the selection of complementary cancer therapy regimens [38]. These topics were not evaluated in this study. Likewise, it is known that cancer survival is associated not only to primary malignancy but also to concomitant nonmalignant diseases. In this sense, comorbidity may play an important role in the prognosis of these patients and this was observed in our study. Charlson Comorbidity Index recorded in our series, and other comorbidity scores, may help to provide a good prognostic prevision of prospective outcome of colorectal cancer patients undergoing surgery [40]. Perhaps the most determining variable in predicting overall survival is tumor stage [15,20]. In our study, the possibility of dying according to the tumor stage increased by 80% as the value of the stage increased.

Some prognostic nomograms have been reported for predicting long-term outcomes after colorectal cancer surgery. Kong et al. [41] developed an interesting survival nomogram based on the relative weights of T stage and N stage, which were calculated based on the analysis of their impact on survival in non-metastatic colorectal cancer in the Surveillance, Epidemiology, and End Results (SEER) database. Yu and Zhang [42] established an overall survival and cancer-specific nomograms for colorectal cancer patients older than 70 years. They included as variables sex, age, marital status, grade, TNM, tumor size, and presence of different metastasis in their overall survival nomogram. Tumor site and SEER stage were added in the cancer-specific survival nomogram. Zhang et al. [43] included size, extent, grade, site, gender, marital status, histology, lymph node count, CEA, race, depth, lymph node ratio, metastasis, and age as variables for both, overall survival and cancer-specific survival nomograms. Zheng et al. [44], in their nomogram for elderly patients with stages I-III colon cancer, involved the variables grade, T stage, N stage, colectomy, and CEA. Finally, Wang et al. [45], added chemotherapy to the variables age, race, primary site, grade, T stage,

and N stage.

It should be noted that none of these predictor nomograms included postoperative complications.

Based on our results, we designed a prognostic score, the S-CRC-PC, which included age, comorbidity measured by Charlson comorbidity index, postoperative complications graded by CCI, and TNM tumor stage as predictor variables. All these variables were independent prognostic factors for survival in the multivariate analysis. To our knowledge, this is the first prognostic index of long-term survival after colorectal surgery for cancer, which includes postoperative complications measured by the CCI.

According to this index, the values which were obtained and grouped into the three categories of low (0–8 points), intermediate (8.1–16 points), and high risk of death during the follow-up (>16 points), were very good predictors of long-term survival. Therefore, we believe that this score may be very useful to tailor postoperative counselling of patients undergoing colorectal surgery for cancer.

This study was subject to the usual limitations of a single center design, which might decrease the generalizability of the results. A series of emerging biomarkers such as KRAS mutation or BRAF mutation have also not been included. Furthermore, the score has not yet been externally validated. Despite this, we consider the data to be of high quality. Our database was prospectively collected from consecutive patients, and the assessment of postoperative complication was carefully recorded.

5. Conclusions

Postoperative complications after colorectal cancer surgery assessed by CCI are associated with adverse oncologic outcomes. Efforts to reduce both the incidence and severity of complications are needed to improve long-term survival in these patients. The S-CRC-PC score may be helpful in predicting long-term cancer outcomes.

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Eva Nogués-Ramía: Data acquisition, Manuscript editing, Manuscript review.

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Manuel Artiles-Armas: Data acquisition, Manuscript editing, Manuscript review.

Cristina Roque-Castellano: Conceptualization, Data analysis and interpretation, Manuscript editing, Manuscript review.

Declaration of competing interest

None

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References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, 2021, CA, Cancer J. Clin. 71 (2021) 7–33, https://doi.org/10.3322/caac.21654.

[2] R.L. Siegel, K.D. Miller, A. Goding Sauer, S.A. Fedewa, L.F. Butterly, J.C. Anderson, A. Cercek, R.A. Smith, A. Jemal, Colorectal cancer statistics, 2020, CA A Cancer J. Clin. 70 (2020) 145–164, https://doi.org/10.3322/caac.21601.

[3] I. van den Berg, R.R.J. Coebergh van den Braak, J.L.A. van Vugt, J.N.M. Ijzermans, S. Buettner, Actual survival after resection of primary colorectal cancer: results from a prospective multicenter study, World J. Surg. Oncol. 191 (19) (2021) 1–10, https://doi.org/10.1186/S12957-021-02207-4, 2021.

[4] R. Gupta, S. Sinha, R.N. Paul, The impact of microsatellite stability status in colorectal cancer, Curr. Probl. Cancer 42 (2018) 548–559, https://doi.org/10.1016/j.currproblcancer.2018.06.010.

[5] B. Mitrovic, K. Handley, N. Assarzadegan, H.L. Chang, H.A.E. Dawson, A. Grin, G. G.A. Hutchins, L. Magill, P. Quirke, R.H. Riddell, R.G. Gray, R. Kirsch, Prognostic and predictive value of tumor budding in colorectal cancer, Clin. Colorectal Cancer 20 (2021) 256–264, https://doi.org/10.1016/j.clcc.2021.05.003.

[6] M. Skancke, S.M. Arnott, R.L. Amdur, R.S. Siegel, V.J. Obias, B.A. Umapathi, Lymphovascular invasion and perineural invasion negatively impact overall survival for stage II adenocarcinoma of the colon, Dis. Colon Rectum 62 (2019) 181–188, https://doi.org/10.1097/DCR.0000000000001258.

[7] S.S. Coughlin, Social determinants of colorectal cancer risk, stage, and survival: a systematic review, Int. J. Colorectal Dis. 35 (2020) 985–995, https://doi.org/10.1007/s00384-020-03585-z.

[8] M. Yahagi, K. Okabayashi, H. Hasegawa, M. Tsuruta, Y. Kitagawa, The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis, J. Gastrointest. Surg. 20 (2016) 648–655, https://doi.org/10.1007/s11605-015-3026-6.

[9] M. Hashimoto, N. Uesugi, M. Osakabe, N. Yanagawa, K. Otsuka, Y. Kajiwara, H. Ueno, A. Sasaki, T. Sugai, Expression patterns of microenvironmental factors and tenascin-C at the invasive front of stage II and III colorectal cancer: novel tumor prognostic markers, Front. Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.690816.

[10] G. Lech, R. Słotwiński, M. Słodkowski, I.W. Krasnodębski, Colorectal cancer tumour markers and biomarkers: recent therapeutic advances, World J. Gastroenterol. 22 (2016) 1745–1755, https://doi.org/10.3748/wjg.v22.i5.1745.

[11] C. Chen, Y. Liu, P. Han, B. Cui, Research progress of preoperative FPR, FAR or AFR in patients with colorectal cancer, Cancer Manag. Res. 13 (2021) 1791–1801, https://doi.org/10.2147/CMAR.S292605.

[12] E. Puerta-Garcia, M. Canadas-Garre, M.A. Calleja-Hernandez, Molecular biomarkers in colorectal carcinoma, Pharmacogenomics 16 (2015) 1189–1222, https://doi.org/10.2217/PGS.15.63.

[13] M. Ishizuka, N. Shibuya, K. Takagi, H. Hachiya, K. Tago, S. Sato, T. Shimizu, T. Matsumoto, T. Aoki, K. Kubota, Impact of anastomotic leakage on postoperative survival of patients with colorectal cancer: a meta-analysis using propensity score matching studies, Surg. Oncol. 37 (2021), 101538, https://doi.org/10.1016/j.suronc.2021.101538.

[14] L.C. Duraes, L. Stocchi, S.R. Steele, M.F. Kalady, J.M. Church, E. Gorgun, D. Liska, H. Kessler, O.A. Lavryk, C.P. Delaney, The relationship between clavien–dindo morbidity classification and oncologic outcomes after colorectal cancer resection, Ann. Surg Oncol. 25 (2018) 188–196, https://doi.org/10.1245/s10434-017-6142-6.

[15] C. Beck, K. Weber, M. Brunner, A. Agaimy, S. Semrau, R. Grützmann, V. Schellerer, S. Merkel, The influence of postoperative complications on long-term prognosis in patients with colorectal carcinoma, Int. J. Colorectal Dis. 35 (2020) 1055–1066, https://doi.org/10.1007/s00384-020-03557-3.

[16] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey, Ann. Surg. 240 (2004) 205–213. https://www.ncbi.nlm.nih.gov/pubmed/15273542.

[17] K. Slankamenac, R. Graf, J. Barkun, M.A. Puhan, P.A. Clavien, The comprehensive complication index: a novel continuous scale to measure surgical morbidity, Ann. Surg. 258 (2013) 1–7, https://doi.org/10.1097/SLA.0b013e318296c732.

[18] K. Slankamenac, N. Nederlof, P. Pessaux, J. De Jonge, B.P.L. Wijnhoven, S. Breitenstein, C.E. Oberkofler, R. Graf, M.A. Puhan, P.A. Clavien, The comprehensive complication index a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials, Ann. Surg. 260 (2014) 757–763, https://doi.org/10.1097/SLA.0000000000000948.

[19] D. Wang, J. Zhang, Z. Bai, Y. Yang, T. Wang, L. Jin, J. Wang, G. Wu, T. Kou, Z. Zhang, Associations of Postoperative Complications Assessed by Clavien-Dindo Classification and Comprehensive Complication Index with Long-Term Overall Survival in Elderly Patients after Radical CRC Resection, 2020, https://doi.org/10.2147/CIA.S271969.

[20] K. Slankamenac, M. Slankamenac, A. Schlegel, A. Nocito, A. Rickenbacher, P. A. Clavien, M. Turina, Impact of postoperative complications on readmission and long-term survival in patients following surgery for colorectal cancer, Int. J. Colorectal Dis. 32 (2017) 805–811, https://doi.org/10.1007/s00384-017-2811-y.

[21] D. Brierley, M. Gospodarowicz, C. Wittekind (Eds.), TNM Classification of Malignant Tumors, eighth ed., Wiley Blackwell, 2017 https://doi.org/10.1177/003591571400702073.

[22] M. Charlson, T.P. Szatrowski, J. Peterson, J. Gold, Validation of a combined comorbidity index, J. Clin. Epidemiol. 47 (1994) 1245–1251. https://www.ncbi.nlm.nih.gov/pubmed/7722560.

[23] M.R. Weiser, AJCC 8th edition: colorectal cancer, ann, Surg. Oncol. 25 (2018) 1454–1455, https://doi.org/10.1245/s10434-018-6462-1.

[24] P.A. Clavien, D. Vetter, R.D. Staiger, K. Slankamenac, T. Mehra, R. Graf, M. A. Puhan, The comprehensive complication index (CCI ®): added value and clinical perspectives 3 years "down the line, Ann. Surg. 265 (2017) 1045–1050, https://doi.org/10.1097/SLA.0000000000002132.

[25] J.D. Smith, P.B. Paty, J.G. Guillem, L.K. Temple, M.R. Weiser, G.M. Nash, Anastomotic leak is not associated with oncologic outcome in patients undergoing low anterior resection for rectal cancer, Ann. Surg. 256 (2012), https://doi.org/10.1097/SLA.0b013e318257d2c1.

[26] M. Ishizuka, N. Shibuya, K. Takagi, H. Hachiya, K. Tago, S. Sato, T. Shimizu, T. Matsumoto, T. Aoki, K. Kubota, Impact of anastomotic leakage on postoperative survival of patients with colorectal cancer: a meta-analysis using propensity score matching studies, Surg. Oncol. 37 (2021), 101538, https://doi.org/10.1016/j.suronc.2021.101538.

[27] A. Artinyan, S.T. Orcutt, D.A. Anaya, P. Richardson, G.J. Chen, D.H. Berger, Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients, Ann. Surg. 261 (2015) 497–505, https://doi.org/10.1097/SLA.0000000000000854.

[28] R.H. Tu, J.X. Lin, P. Li, J.W. Xie, J. Bin Wang, J. Lu, Q.Y. Chen, L. long Cao, M. Lin, C.H. Zheng, C.M. Huang, Comprehensive complication index predicts cancer-specific survival of patients with postoperative complications after curative resection of gastric cancer, Gastroenterol. Res. Pract. (2018), https://doi.org/10.1155/2018/4396018, 2018.

[29] K. Slankamenac, R. Graf, J. Barkun, M.A. Puhan, P.-A. Clavien, The comprehensive complication index, Ann. Surg. 258 (2013), https://doi.org/10.1097/SLA.0b013e318296c732.

[30] S. Yamashita, R.A. Sheth, A.S. Niekamp, T.A. Aloia, Y.S. Chun, J.E. Lee, J. N. Vauthey, C. Conrad, Comprehensive complication index predicts cancer-specific survival after resection of colorectal metastases independent of RAS mutational status, Ann. Surg. 266 (2017) 1045–1054, https://doi.org/10.1097/SLA.0000000000002018.

[31] M.C. Fernández-Moreno, D. Dorcaratto, M. Garcés-Albir, E. Muñoz, R. Arvizu, J. Ortega, L. Sabater, Impact of type and severity of postoperative complications on long-term outcomes after colorectal liver metastases resection, J. Surg. Oncol. 122 (2020) 212–225, https://doi.org/10.1002/jso.25946.

[32] M.K. Angele, E. Faist, Clinical review: immunodepression in the surgical patient and increased susceptibility to infection, Crit. Care 6 (2002), https://doi.org/10.1186/cc1514.

[33] C. Sietses, R.H.J. Beelen, S. Meijer, M.A. Cuesta, Immunological consequences of laparoscopic surgery, speculations on the cause and clinical implications, Langenbeck's Arch. Surg. 384 (1999), https://doi.org/10.1007/s004230050200.

[34] Y. Goldfarb, L. Sorski, M. Benish, B. Levi, R. Melamed, S. Ben-Eliyahu, Improving postoperative immune status and resistance to cancer metastasis, Ann. Surg. 253 (2011), https://doi.org/10.1097/SLA.0b013e318211d7b5.

[35] H. Saeki, S. Tsutsumi, H. Tajiri, T. Yukaya, R. Tsutsumi, S. Nishimura, Y. Nakaji, K. Kudou, S. Akiyama, Y. Kasagi, R. Nakanishi, Y. Nakashima, M. Sugiyama, K. Ohgaki, H. Sonoda, E. Oki, Y. Maehara, Prognostic significance of postoperative complications after curative resection for patients with esophageal squamous cell carcinoma, Ann. Surg. 265 (2017) 527–533, https://doi.org/10.1097/SLA.0000000000001692.

[36] L. Sánchez-Guillén, L. Soriano-Irigaray, F. López-Rodríguez-arias, X. Barber, A. Murcia, M.J. Alcaide, V. Aranaz-Ostáriz, Á. Soler-Silva, A. Navarro-Ruiz, A. Arroyo, Effect of early peripheral parenteral nutrition support in an enhanced recovery program for colorectal cancer surgery: a randomized open trial, J. Clin. Med. 10 (2021), https://doi.org/10.3390/jcm10163647.

[37] P. Gao, X. zhang Huang, Y. xi Song, J. xu Sun, X. wan Chen, Y. Sun, Y. meng Jiang, Z. ning Wang, Impact of timing of adjuvant chemotherapy on survival in stage III colon cancer: a population-based study, BMC Cancer 18 (2018), https://doi.org/10.1186/s12885-018-4138-7.

[38] F. Chen, F. Wang, C.E. Bailey, H.J. Murff, J.D. Berlin, X.-O. Shu, W. Zheng, Evaluation of determinants for age disparities in the survival improvement of colon cancer: results from a cohort of more than 486,000 patients in the United States, Am. J. Cancer Res. 10 (2020) 3395–3405. www.ajcr.us/. (Accessed 13 October 2021).

[39] M. Artiles-Armas, C. Roque-Castellano, A. Conde-Martel, J. Marchena-Gómez, The comprehensive complication index is related to frailty in elderly surgical patients, J. Surg. Res. 244 (2019) 218–224, https://doi.org/10.1016/j.jss.2019.06.011.

[40] S. Marventano, G. Grosso, A. Mistretta, M. Bogusz-Czerniewicz, R. Ferranti, F. Nolfo, G. Giorgianni, S. Rametta, F. Drago, F. Basile, A. Biondi, Evaluation of four comorbidity indices and Charlson comorbidity index adjustment for colorectal cancer patients, Int. J. Colorectal Dis. 29 (2014) 1159–1169, https://doi.org/10.1007/s00384-014-1972-1.

[41] X. Kong, J. Li, Y. Cai, Y. Tian, S. Chi, D. Tong, Y. Hu, Q. Yang, J. Li, G. Poston, Y. Yuan, K. Ding, A modified TNM staging system for non-metastatic colorectal cancer based on nomogram analysis of SEER database, BMC Cancer 18 (2018), https://doi.org/10.1186/s12885-017-3796-1.

[42] C. Yu, Y. Zhang, Establishment of prognostic nomogram for elderly colorectal cancer patients: a SEER database analysis, BMC Gastroenterol. 20 (2020), https://doi.org/10.1186/s12876-020-01464-z.

[43] Z. yu Zhang, Q. feng Luo, X. wei Yin, Z. ling Dai, S. Basnet, H. yan Ge, Nomograms to predict survival after colorectal cancer resection without preoperative therapy, BMC Cancer 16 (2016), https://doi.org/10.1186/s12885-016-2684-4.

[44] P. Zheng, C. Lai, W. Yang, J. Guo, S. Xiao, Z. Chen, Nomogram predicting cancer-specific survival in elderly patients with stages I–III colon cancer, Scand. J. Gastroenterol. 55 (2020) 202–208, https://doi.org/10.1080/00365521.2020.1720280.

[45] S. Wang, Y. Liu, Y. Shi, J. Guan, M. Liu, W. Wang, Development and external validation of a nomogram predicting overall survival after curative resection of colon cancer, J. Int. Med. Res. 49 (2021), https://doi.org/10.1177/03000605211015023.

ARTICULO II

“Utility of C-reactive protein on the fourth postoperative day to detect complications beyond anastomotic dehiscence”

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RESEARCH

Utility of C-reactive protein on the fourth postoperative day to detect complications beyond anastomotic dehiscence

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Abstract

Purpose Postoperative complications can affect recovery after colorectal cancer surgery. Elevated C-reactive protein (CRP) levels have been studied as a predictor of anastomotic dehiscence, but evidence regarding its association with overall complications is limited. This study aimed to explore the link between CRP levels on the fourth postoperative day and overall postoperative complications using the comprehensive complication index (CCI).

Methods The observational study included 935 patients who underwent colorectal cancer surgery between 2015 and 2022. Patients were categorized into three groups: no complications, complications excluding dehiscence, and complications with dehiscence. The relationship between CRP levels and postoperative complications was analyzed, and the optimal CRP cutoff point was determined.

Results The median CRP values were 34.3 (20.4–54.0) mg/L in the group with no complications, 69.9 (43.2–112.9) mg/L in the group with complications excluding dehiscence, and 167.6 (69.7–239.5) mg/L in patients with dehiscence. A significant correlation between CRP levels and postoperative complications was found ($p < 0.001$). Based on the identified cutoff points, CRP levels above 58 mg/L suggest the presence of any complication, including dehiscence. Levels between 42 and 58 mg/L suggest complications excluding dehiscence, and levels below 42 mg/L strongly exclude complications, with a negative predictive value of 82%.

Conclusions Elevated CRP on postoperative day 4 is associated with overall postoperative complications, not just dehiscence. A positive correlation exists between CCI score and CRP levels. A CRP value < 42 mg/L on day 4 allows clinicians to reliably exclude the presence of any complication.

Keywords Colorectal cancer · C-reactive protein · Postoperative complications · Anastomotic dehiscence · Comprehensive complication index

Introduction

Colorectal cancer is the second leading cause of cancer-related mortality, with an overall 5-year survival rate of 64% [1]. The prognosis of the disease is better in patients diagnosed at early stages and those who can undergo surgery [2].

Colorectal cancer surgery carries a non-negligible morbidity and mortality rate which may impact long-term survival, although there are contradictory findings in the scientific literature [3–5]. Therefore, it is important to minimize the occurrence of postoperative complications and their impact on the patient.

There is considerable scientific evidence regarding the role of postoperative analytical parameters in predicting the onset of postoperative complications [6]. Primarily, the relationship between C-reactive protein (CRP) levels and anastomotic dehiscence has been studied [7].

However, there is limited evidence regarding whether changes in CRP are associated with the occurrence of overall postoperative complications, in addition to anastomotic dehiscence. The studies that investigate this typically rely on

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the Clavien-Dindo classification [8]. Fewer data are available on this relationship using the comprehensive complication index (CCI) [9], which may be more useful for assessing the overall severity of all postoperative complications [10].

This study aimed to analyze the relationship between elevated CRP levels on the fourth postoperative day (CRP-4POD) and the occurrence of postoperative complications according to the CCI classification. Additionally, we aimed to compare the elevation of CRP-4POD levels based on whether the postoperative complication was anastomotic dehiscence or another complication unrelated to dehiscence.

Methods

Study design

This was a retrospective, observational, and longitudinal study that included 935 patients who underwent surgery for colorectal cancer at our institution between January 2015 and December 2022. All patients diagnosed with colorectal cancer were included, regardless of stage, provided they were treated with curative intention. Patients who underwent emergency surgery for complicated colorectal cancer were excluded.

This study was performed in line with the principles of the Declaration of Helsinki [11] and reported according to the STROBE guidelines [12]. Approval was granted by the Clinical Ethics and Research Committee of the institution (2020–279-1).

Patient management

The diagnosis was made through colonoscopy and biopsy, while staging was performed using thoracoabdominal computed tomography (CT) and pelvic magnetic resonance imaging (MRI) for patients diagnosed with rectal cancer. The stage was determined according to the 8 th edition of the AJCC TNM classification [13].

Patients were admitted the day before surgery, and a baseline analytical assessment including a complete blood count was performed. All patients underwent mechanical bowel preparation with oral antibiotics.

Surgery was performed by specialist colorectal surgeons, with most procedures being minimally invasive (laparoscopic and robotic surgery). The anastomosis technique was carried out using mechanical suturing devices.

Postoperatively, CRP levels were measured on the fourth day after surgery in all patients, and the results were expressed in mg/L.

The entire series was followed up for a median of 43.8 months (IQR, 23.4–69.4).

Study groups

The sample was divided into three groups: patients without complications, patients with complications without anastomotic dehiscence, and patients with complications that included anastomotic dehiscence.

Study variables

The following variables were collected:

- Demographic variables: age and sex.
- Comorbidity: Charlson Comorbidity Index. Comorbidity was stratified as low (0–2 points), moderate (3–4 points), and high (> 4 points).
- Tumor characteristics: location and tumor stage.
- Surgical variables: type of approach, conversion, type of surgery performed.
- Postoperative outcomes: postoperative complications with special attention to anastomotic dehiscence, reoperations, operative mortality, and postoperative length of stay (in days). Postoperative complications were scored using the comprehensive complication index (CCI), which is based on Clavien-Dindo and takes into account all adverse event. The score ranges from 0 (no complications) to 100 points (death). The CCI was subdivided into four groups: no complications (0 points), mild complications (1–26.1 points), moderate complications (26.2–42.2 points), and severe complications (> 42.3 points) [14]. The score was calculated using the following online tool: https://www.assessurgery.com/about_cci-calculator/.
- Operative mortality was defined as deaths occurring within the first 90 days after surgery or later if they were directly caused by a postoperative complication.

Statistical analysis

The data were analyzed using the statistical software suite SPSS 29.0 for Windows (IBM Corporation, Armonk, NY, USA) and the software Jamovi 2.3 (The Jamovi Project, 2022).

First, a descriptive analysis of the sample was performed. Categorical variables were expressed as frequencies and percentages. Numeric variables were expressed as means (± standard deviation) (SD) or medians (interquartile range) (IQR), depending on whether the distribution followed a normal distribution. The Kolmogorov–Smirnov test was used to assess normality.

Next, a comparative study was conducted between the three study groups, analyzing the differences observed in CRP values and CCI scores for each group. The Kruskal–Wallis test was used for this, and the Spearman's correlation coefficient was used to assess the relationship between CRP and CCI. Finally, the diagnostic performance of CRP in relation to CCI was analyzed in two scenarios: in the entire sample and in a sample of patients from which anastomotic dehiscences were excluded. Receiver operating characteristic (ROC) curves were constructed for each scenario to determine the respective cutoff points based on the Youden index [15], which represents the point of maximum sensitivity and specificity. Sensitivity, specificity, positive predictive value, and negative predictive value of CRP were then calculated for each scenario.

To evaluate the influence of the type of surgery (colonic vs rectal surgery) as a potential confounder in relation to postoperative CRP levels, a multivariable linear regression analysis was conducted. The model included complication type (no complications, complications without dehiscence, dehiscence) and was adjusted for surgery type (colonic vs rectal). The outcome variable was CRP-4POD. Variance inflation factors (VIFs) were computed to assess and exclude multicollinearity.

A significance level of $p < 0.05$ was considered.

Results

The results of the descriptive analysis of the 935 patients included in the study are shown in Table 1.

Of the 935 patients, 308 (32.95%) had some type of complication, most of which were mild complications, with a CCI < 26.2 (152 patients, 16.26%).

Regarding the type of complication, 51 cases (5.5%) of anastomotic leakage were identified, along with 65 hemorrhagic complications (6.9%), of which 32 patients (3.4%) required red blood cell transfusion. Postoperative adynamic ileus was observed in 118 patients (12.6%), with 62 (6.6%) requiring parenteral nutrition. Additionally, 35 cases (3.7%) of surgical wound infections, 26 (2.78%) intra-abdominal collections, and 12 (1.28%) cases of evisceration were recorded.

Among non-abdominal complications, 39 patients (4.17%) developed infectious complications related to central venous access, 37 (3.96%) experienced respiratory complications, 23 (2.46%) presented with cardiological complications, and 52 patients (5.56%) had nephrourological complications.

A further 65 patients (6.95%) experienced other types of complications, including non-infectious surgical wound issues such as seromas or hematomas in 21 cases (2.2%), superficial infections of peripheral venous

Table 1 Demographic characteristics

Sex	
Male	585 (62.6%)
Female	350 (37.4%)
Age (median–IQR)	70 years (62.0–77.0)
Comorbidity (Charlson Index)	
Low	442 (47.27%)
Moderate	356 (38.07%)
High	137 (14.66%)
TNM stage	
I	219 (23.42%)
II	340 (36.37%)
III	308 (32.94%)
IV	68 (7.27%)
Tumor location	
Colon	669 (71.55%)
Rectum	266 (28.45%)
Specific location	
Right colon	306 (32.74%)
Left colon	81 (8.66%)
Sigmoid colon	212 (22.67%)
Upper rectum	75 (8.02%)
Medium rectum	128 (13.69%)
Low rectum	66 (7.05%)
Synchronic tumors	18 (1.93%)
Surgical technique	
Right colectomy	322 (34.44%)
Left colectomy	75 (8.02%)
Sigmoidectomy	196 (20.96%)
Upper anterior rectal resection	82 (8.77%)
Low anterior rectal resection	139 (14.87%)
Ultra-low anterior rectal resection	34 (3.64%)
Segmentary colectomy	40 (4.28%)
Total colectomy	18 (1.93%)
Combined resection	7 (0.74%)
Abdominoperineal amputation	22 (2.35%)
Surgical approach	
Open surgery	269 (28.77%)
Laparoscopic surgery	554 (59.25%)
Robotic surgery	112 (11.98%)
Conversion	
Yes	47 (7.06%)
No	619 (92.94%)
Length of stay	
Mean (± SD)	8.7 days (7.6)
Median (IQR)	6 days (5.0–9.3)
Postoperative complication	
No	627 (67.05%)
Yes	308 (32.95%)
CCI	
0	627 (67.05%)
1–26.2	152 (16.26%)

Table 1 (continued)

26.3–42.2	83 (8.88%)
> 42.2	73 (7.81%)
Type of complication	
Anastomotic dehiscence	51 (5.5%)
Hemorrhagic complication	65 (6.9%)
Adynamic ileus	118 (12.6%)
Surgical wound infection	35 (3.7%)
Intraabdominal collection	26 (2.78%)
Evisceration	12 (1.28%)
Central venous access related infection	39 (4.17%)
Cardiological complication	23 (2.46%)
Respiratory complication	37 (3.96%)
Nephro-urological complication	52 (5.56)
Other complication	65 (6.95%)
Readmission	38 (4.1%)
Reoperation	85 (9.1%)
Postoperative mortality	9 (1%)

access in 15 cases (1.6%), ostomy-related problems in 12 patients (1.28%), and visceral perforation or intestinal obstruction requiring reoperation in 11 patients (1.18%).

Of the entire cohort, 38 patients (4.1%) were readmitted within 30 days of hospital discharge, 85 (9.1%) required reoperation due to complications related to the initial procedure, and 9 patients (1.0%) died within 90 days following surgery.

The mean CRP-4POD value for the entire sample was 62.28 (± 62.57) mg/L, with a median of 42.14 (IQR, 24.81–73.52) mg/L. The mean CCI score was 10.51 (± 18.77) points, with a median of 0.00 (IQR, 0.00–20.90) points. A very significant correlation was found between CRP levels on the fourth postoperative day and postoperative complications according to the CCI ($p < 0.001$) (Fig. 1).

The median CRP-4POD values were 34.3 (20.4–54.0) mg/L for the 627 patients in the group with no complications, 69.9 (43.2–112.9) mg/L for the 257 patients in the group with complications excluding dehiscence, and 167.6 (69.7–239.5) mg/L for the 51 patients with dehiscence (Fig. 2). These differences were statistically significant ($p < 0.001$). Pairwise comparisons between the three groups for the CRP-4POD variable (no complications, complications excluding dehiscence, and dehiscence) also showed statistically significant differences for each comparison ($p < 0.001$).

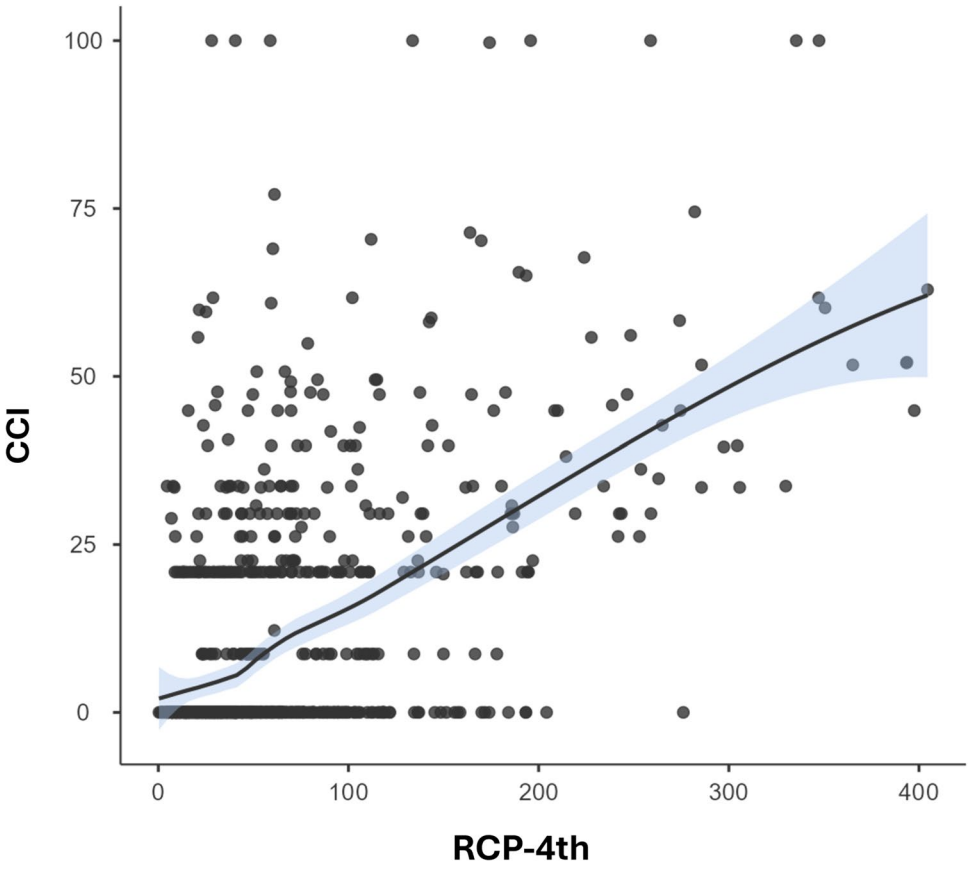

Fig. 1 C-reactive protein on the fourth postoperative day correlation with comprehensive complication index ($p < 0{,}001$)

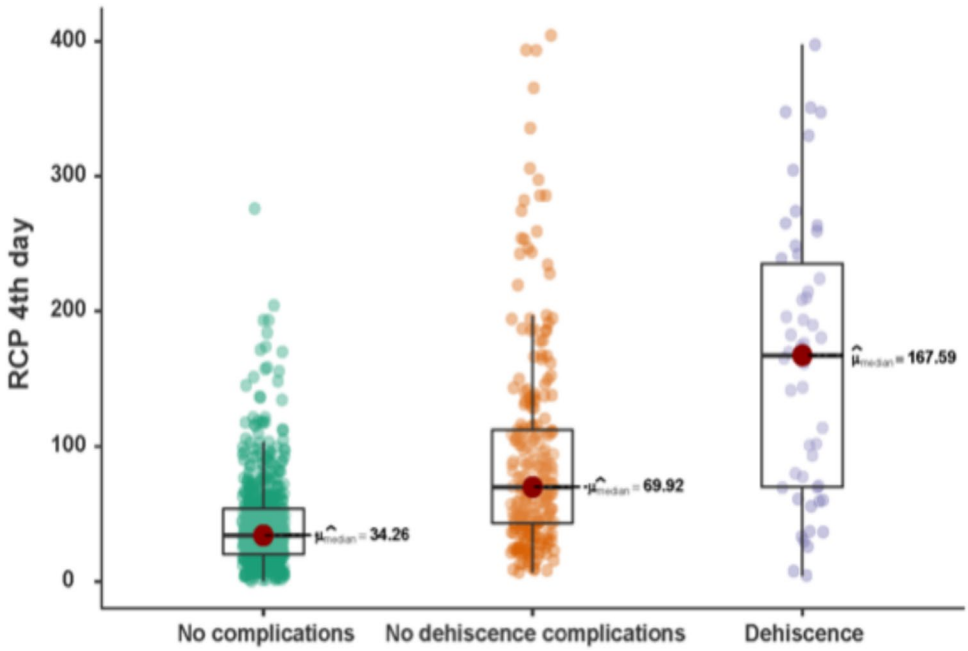

Fig. 2 Differences in C-reactive protein between the no-complication group, the no-dehiscence complication group, and the dehiscence group ($p < 0{,}001$)

In the multivariable analysis, the complication type variable ($p < 0.001$) behaved as an independent prognostic factor for CRP levels on postoperative day 4 (CRP-4POD) after adjustment for surgery type (colonic vs rectal) ($p = 0.917$). No collinearity was detected (VIF = 1.02 for both variables).

Likewise, when categorizing the CCI into no complications (0 points), mild (1–26.1 points), moderate (26.2–42.2 points), and severe (≥ 42.3 points) complications, statistically significant differences were observed in the CRP-4POD levels between all four categories (Fig. 3).

Regarding the diagnostic ability of CRP-4POD to detect any type of complication (CCI = 0 vs CCI = 1), the results are shown in Fig. 4. According to the Youden index, the optimal cutoff point used in the analysis was 58 mg/L. This indicates that a CRP level above 60 mg/L on the fourth postoperative day should raise suspicion of some type of complication, including a potential anastomotic dehiscence. Levels below 60 mg/L exclude anastomotic dehiscence, as well as other complications, with a wide margin of safety.

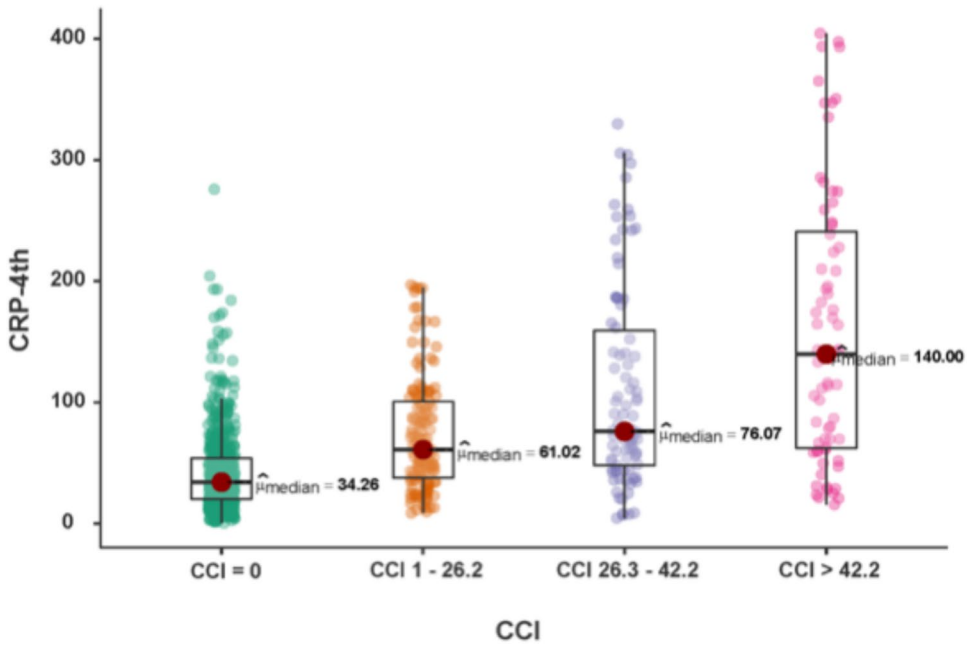

Fig. 3 C-reactive protein comparison between CCI groups: no complications, mild complications, moderate complications, and severe complications ($p < 0{,}001$)

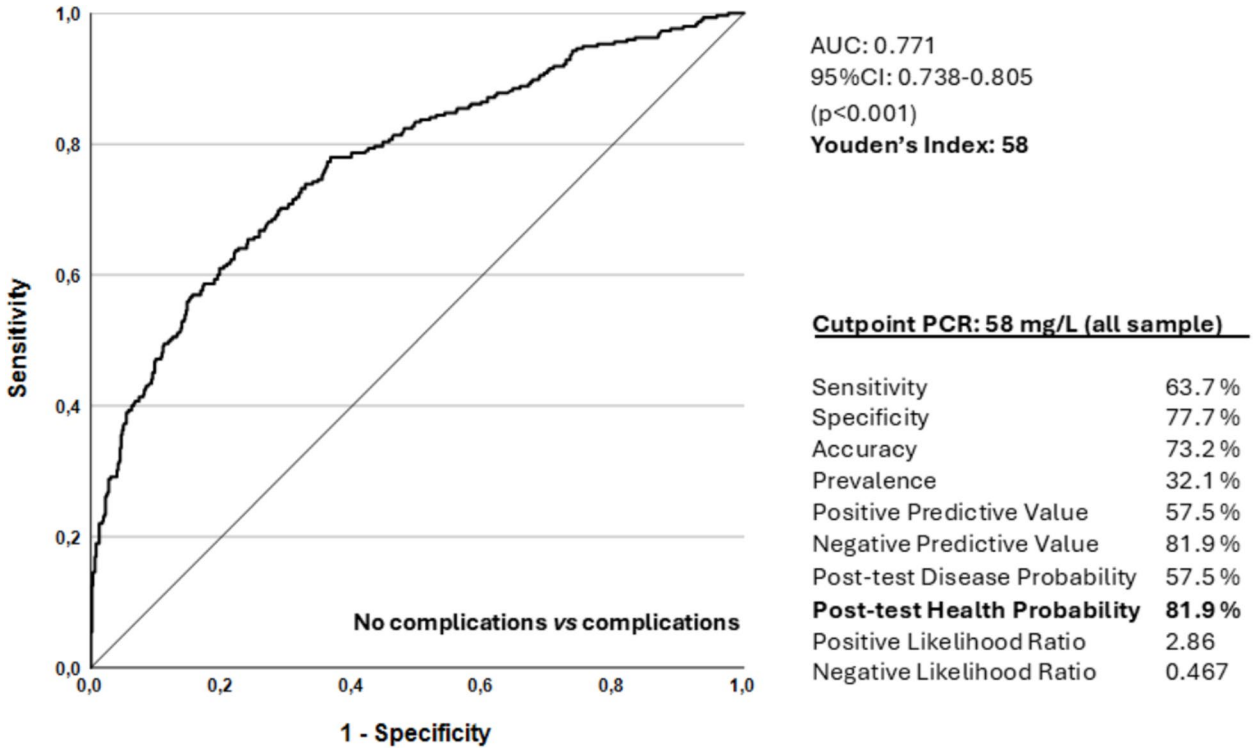

Fig. 4 ROC curve and diagnostic parameters for the identification of patients with complications using a PCR cutoff value of 58 mg/L. AUC 0.771 (95% IC 0.738–0.805, $p < 0.001$)

Regarding the diagnostic ability of CRP-4POD to detect complications unrelated to anastomotic dehiscence (CCI = 0 vs CCI = 1, once patients with dehiscence were excluded from the sample), the results are shown in Fig. 5. In this case, Youden index indicated the optimal cutoff point at 42 mg/L. Therefore, a CRP level between 42 and 60 mg/L may indicate the presence of a complication other than anastomotic dehiscence, and levels below 40 mg/L exclude any type of complication with a wide margin of safety.

Discussion

This study is in line with other publications regarding the relationship between CRP on the fourth postoperative day and anastomotic dehiscence [16–20]. It has also demonstrated its utility in predicting any type of postoperative complication, not just anastomotic dehiscence, as well as a positive correlation between CRP levels and the severity of complications, which are relatively underexplored in the scientific literature.

Among the results, we highlight the clear positive correlation between the absolute values of CCI and CRP, meaning that a higher CRP on the fourth postoperative day was associated with a higher postoperative CCI, and thus greater severity of postoperative complications. A statistically significant association was also observed between CRP-4POD and the CCI categorized from lowest to highest severity. To our knowledge, this analysis in colorectal cancer surgery has not been reported previously in the literature.

However, this association has been indirectly reported in pancreatic cancer surgery. In 2022, Bonsdorff et al. [21] studied the occurrence of pancreatitis following cephalic duodenopancreatectomy and demonstrated that patients who developed pancreatitis with elevated CRP had higher CCI scores compared to those with no CRP elevation, indicating that the complications were more severe.

Our team believes that the comprehensive complication index (CCI), which is based in Clavien-Dindo classification, allows for a specific assessment of the overall severity of all postoperative complications.

Subgroup analyses of CRP and complications have already been performed with the Clavien-Dindo classification, and the results have been similar. In a 2015 study of 241 patients, McSorley et al. [8] compared CRP levels on the second, third, and fourth days with the Clavien-Dindo classification, dividing patients into those with no complications (grade 0), mild complications (grades 1–2), or severe complications (grades 3–5). The mean CRP on the fourth postoperative day was 98 mg/L for patients without complications, 161 mg/L for those with mild complications, and

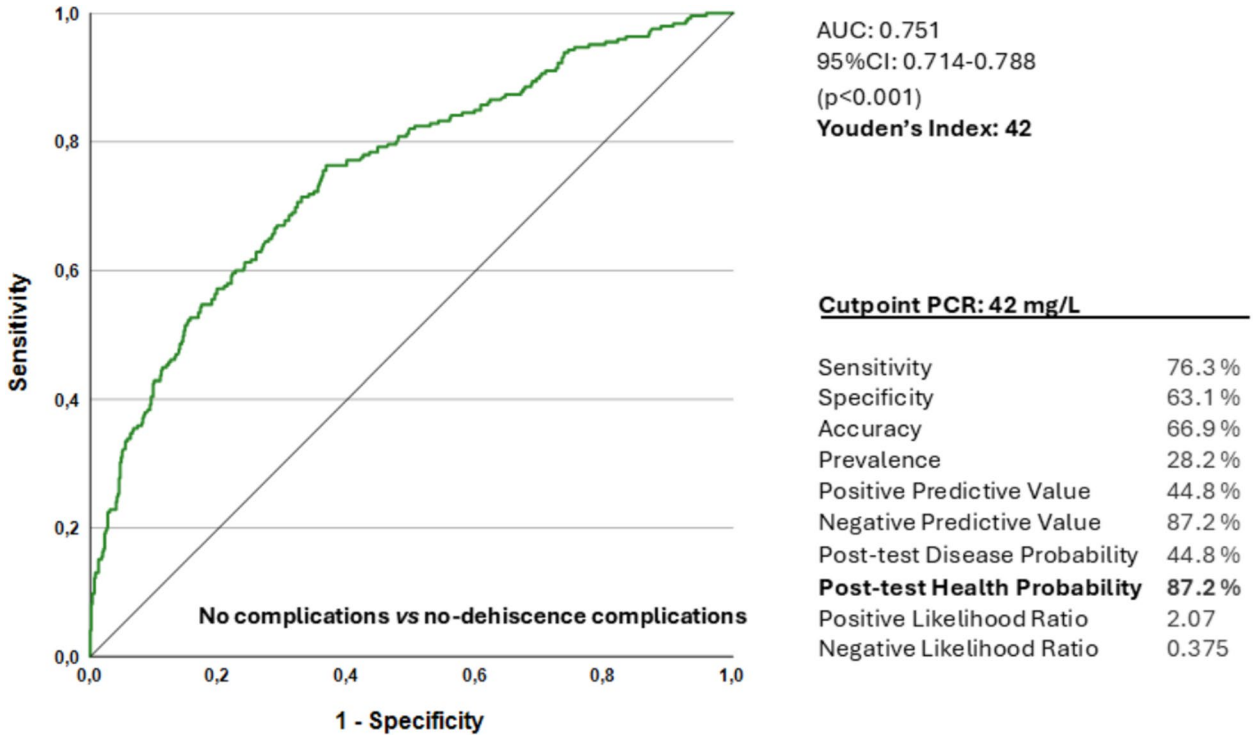

Fig. 5 ROC curve and diagnostic parameters for the identification of patients with no dehiscence complications using a PCR cutoff value of 42 mg/L. AUC 0,751 (95% CI 0.714–0.788, $p < 0.001$)

243 mg/L for those with severe complications, with statistically significant results.

We emphasize that CRP-4POD levels in the subgroup of patients who underwent colorectal cancer surgery excluding those with dehiscence were also statistically significantly related to the occurrence of any type of complication. However, the cutoff point to detect these complications was lower. These data support the hypothesis that CRP is a useful parameter for predicting any type of complication occurring in the postoperative period, not just dehiscence.

Platt et al. [22] divided a series of 454 patients undergoing colorectal cancer surgery into three groups: patients without postoperative complications, patients with infectious complications (including anastomotic dehiscence), and patients with non-infectious complications. It was found that CRP was higher in both complication groups compared to the no complication group, but statistical significance was only observed in the infectious complications group. In our study, which did not analyze infectious complications as a separate group, significant differences were found between the no complication group and both the dehiscence and non-dehiscence complication groups. Significant differences in CRP-4POD levels were also observed between the groups with and without dehiscence complications. We believe that an inflammatory state is not always necessarily associated with infection. Any postoperative alteration could lead to an increase in CRP, as seen with cardiovascular problems [23] and acute kidney failure [24].

Various CRP cutoff points have been established for detecting anastomotic dehiscence. Recent meta-analyses have reported a CRP value on the fourth day of 114 mg/L [25] and 123 mg/L [7]. The EDEN Group's multicenter study describes a cutoff of 119 mg/L with a negative predictive value (NPV) of 97% [19]. In our sample, patients with dehiscence had CRP-4POD levels of 167.6 mg/L. Based on our results, we can state with a high probability (NPV, 81.9%) that patients with CRP < 58 mg/L on the fourth postoperative day will not have postoperative complications and will have a CCI score of 0. However, there is little consensus on the exact CRP value at which we can confidently exclude any type of postoperative complication.

Somewhat higher values have been described by Jin et al. [9] in their series of 335 patients, where a cut-off of CRP > 64.7 mg/L was established for detecting a high CCI score.

The optimal day for CRP measurement in predicting complications remains a subject of debate, since an early assessment with elevated values may lead to a false-negative result in complementary tests [26], while a late assessment may result in an avoidable diagnostic delay. In this study, it was determined on the fourth postoperative day, in line with existing evidence for detecting anastomotic dehiscence on the third or fourth postoperative day, with no significant

differences between studies published over the years [7, 16, 27]. However, these studies were focused on detecting anastomotic dehiscence. Regarding the detection of overall complications, it is suggested that CRP should be measured on the fourth day [28, 29], though we have not found studies comparing the third and fourth postoperative days. McSorley et al. [8] compared CRP measurements on the second, third, and fourth postoperative days. They concluded that all days were useful for predicting the severity of postoperative complications but did not analyze which day was optimal for measurement.

In our study, preoperative CRP was not routinely measured. However, a recent systematic review and meta-analysis of 23 studies involving 7147 patients analyzed whether preoperative CRP levels were related to the occurrence of postoperative complications [30]. It could not be shown that elevated preoperative CRP was associated with anastomotic dehiscence, but it was related to the occurrence of overall complications. The results of this meta-analysis support the theory that changes in the inflammatory state of the body, as measured by CRP, can be useful for predicting postoperative deviations from normality.

Traditionally, the development of complications following colorectal cancer surgery, especially anastomotic dehiscence [31, 32], and the presence of an altered postoperative proinflammatory state [33] have been associated with a worsened oncological prognosis [5]. In contrast, more recent studies conducted by the RectoLeak Study Group [4] suggest that no such association exists. This finding could be explained by an earlier diagnosis and the optimization of therapeutic strategies in recent years. Regarding other postoperative complications and their impact on survival [14], similar outcomes may be expected in the future. As suggested by our study, postoperative CRP levels may be useful for the early diagnosis and management of such complications.

CRP is not the only biomarker that has proven useful in the postoperative monitoring of colorectal cancer. In the PREDICS study [34], both CRP and Procalcitonin (PCT) levels were measured on postoperative days 3 and 5. Similar to our study, the values were compared across three patient groups: those who developed no complications, those who experienced anastomotic leakage, and those who suffered postoperative complications unrelated to anastomotic leakage. The study concluded that CRP levels below 12.5 mg/dL and PCT levels below 2.3 ng/mL on the fifth postoperative day were highly effective in ruling out anastomotic leakage, with a NPV exceeding 98%.

It is plausible that the combined use of multiple biomarkers may be more informative than their isolated assessment. This notion is supported by the iCral Study Group [35], who demonstrated not only that PCT levels greater than 1.01 µg/L on the second postoperative day were superior to CRP in predicting mortality, but also that combining the Dutch Leakage Score [36] with both CRP and PCT improved both the PPV and NPV for the prediction of anastomotic leakage, compared to the combination of the Dutch Leakage Score with CRP alone.

As limitations of this study, we must mention that it is a retrospective, single-center observational study and that no analysis by complication subtype was conducted. However, a strength of this study is that it is a consecutive series of colorectal cancer patients and is one of the first studies to use the CCI scale for analyzing postoperative complications in relation to CRP-4POD. Furthermore, it aimed to analyze all postoperative complications, not just anastomotic dehiscence.

We conclude that CRP levels on the fourth postoperative day are statistically significantly related to the occurrence of any type of postoperative complication, not just anastomotic dehiscence. There is a positive correlation between the CCI score and CRP levels. According to our results, a CRP level <42 mg/L on the fourth postoperative day allows us to exclude the occurrence of postoperative complications.

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Author contributions David Ortiz-López: Conceptualization, Data acquisition, Data analysis and interpretation, Manuscript preparation. Joaquín Marchena-Gómez: Conceptualization, Study design, Data analysis and interpretation, Statistical analysis, Manuscript preparation. Eva Nogués-Ramía: Data acquisition, Manuscript editing, Manuscript review. Yurena Sosa-Quesada: Data acquisition, Data analysis and interpretation, Manuscript editing, Manuscript review. Beatríz Arencibia-Pérez: Data acquisition, Manuscript editing, Manuscript review. Manuel Artiles-Armas: Data acquisition, Manuscript editing, Manuscript review. Julia María Gil-García: Data acquisition, Manuscript editing, Manuscript review. Cristina Roque-Castellano: Conceptualization, Data analysis and interpretation, Manuscript editing, Manuscript review.

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Data availability The datasets generated and/or analyzed during the current study are not publicly available due to ethical and legal restrictions concerning the confidentiality and privacy of human participants, in accordance with the Declaration of Helsinki and the General Data Protection Regulation (EU GDPR). Access to de-identified data may be granted upon reasonable request to the corresponding author, subject to prior approval by the relevant institutional review board and in accordance with applicable data sharing agreements.

Declarations

Ethics approval The study was approved by the institution's Clinical Ethics and Research Committee (*CEI/CEIm Hospital Universitario de Gran Canaria Doctor Negrín 2020–279-1*).

Competing interests The authors declare no competing interests.

References

1. Siegel RL, Giaquinto AN, Jemal A (2024) Cancer statistics. CA Cancer J Clin [Internet]. Jan 17; Available from: http://www.ncbi.nlm.nih.gov/pubmed/38230766
2. van den Berg I, Coebergh van den Braak RRJ, van Vugt JLA, Ijzermans JNM, Buettner S (2021) Actual survival after resection of primary colorectal cancer: results from a prospective multicenter study. World J Surg Oncol 19(1):96
3. Warps AK, Tollenaar RAEM, Tanis PJ, Dekker JWT (2022A) Postoperative complications after colorectal cancer surgery and the association with long-term survival. Eur J Surg Oncol 48(4):873–882
4. Gerdin A, Park J, Häggström J, Segelman J, Matthiessen P, Lydrup ML et al (2024) Anastomotic leakage after resection for rectal cancer and recurrence-free survival in relation to postoperative C-reactive protein levels. Int J Colorectal Dis 39(1):193
5. Ishizuka M, Shibuya N, Takagi K, Hachiya H, Tago K, Sato S et al (2021) Impact of anastomotic leakage on postoperative survival of patients with colorectal cancer: a meta-analysis using propensity score matching studies. Surg Oncol 37
6. Alsaif SH, Rogers AC, Pua P, Casey PT, Aherne GG, Brannigan AE et al (2021) Preoperative C-reactive protein and other inflammatory markers as predictors of postoperative complications in patients with colorectal neoplasia. World J Surg Oncol 19(1):74
7. Yeung DE, Peterknecht E, Hajibandeh S, Hajibandeh S, Torrance AW (2021) C-reactive protein can predict anastomotic leak in colorectal surgery: a systematic review and meta-analysis. Int J Colorectal Dis 36(6):1147–1162
8. McSorley ST, Ramanathan ML, Horgan PG, McMillan DC (2015) Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer. Int J Colorectal Dis 30(7):913–917
9. Jin HY, Hong I, Bae JH, Lee CS, Han SR, Lee YS et al (2021) Predictive factors of high comprehensive complication index in colorectal cancer patients using Enhanced Recovery After Surgery protocol: role as a safety net in early discharge. Ann Surg Treat Res 101(6):340
10. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA (2013) The comprehensive complication index. Ann Surg 258(1)
11. World Medical Association Declaration of Helsinki (2013) JAMA 310(20):2191
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2007) Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 335(7624):806–808
13. Weiser MR (2018) AJCC 8th edition: colorectal cancer. Annals of Surgical Oncology. Springer New York LLC p. 25:1454–5
14. Ortiz-López D, Marchena-Gómez J, Nogués-Ramía E, Sosa-Quesada Y, Arencibia-Pérez B, Artiles-Armas M et al (2022) Utility of a new prognostic score based on the Comprehensive Complication Index (CCI®) in patients operated on for colorectal cancer (S-CRC-PC score). Surg Oncol 1:42
15. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3(1)
16. Singh PP, Zeng ISL, Srinivasa S, Lemanu DP, Connolly AB, Hill AG (2014) Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. British Journal of Surgery p. 101:339–46
17. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC (2015) Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg 102(5):462–479
18. Facy O, Paquette B, Orry D, Binquet C, Masson D, Bouvier A et al (2016) Diagnostic Accuracy of Inflammatory Markers As Early Predictors of Infection After Elective Colorectal Surgery. Ann Surg 263(5):961–966
19. Sala Hernandez A, Frasson M, García-Granero A, Hervás Marín D, Laiz Marro B, Alonso Pardo R et al (2021) Diagnostic accuracy of C-reactive protein, procalcitonin and neutrophils for the early detection of anastomotic leakage after colorectal resection: a multicentric, prospective study. Colorectal Dis 23(10):2723–2730
20. Garcia-Granero A, Frasson M, Flor-Lorente B, Blanco F, Puga R, Carratalá A et al (2013) Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery. Dis Colon Rectum 56(4):475–483
21. Bonsdorff A, Helanterä I, Tarvainen T, Sirén J, Kokkola A, Sallinen V (2022) Prediction and consequences of postoperative pancreatitis after pancreaticoduodenectomy. BJS Open 8;6(2)
22. Platt JJ, Ramanathan ML, Crosbie RA, Anderson JH, McKee RF, Horgan PG et al (2012) C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. Ann Surg Oncol 19(13):4168–4177
23. Singh TP, Morris DR, Smith S, Moxon JV, Golledge J (2017) Systematic review and meta-analysis of the association between c-reactive protein and major cardiovascular events in patients with peripheral artery disease. Eur J Vasc Endovasc Surg 54(2):220–233
24. Ota E, Watanabe J, Suwa H, Hirai T, Suwa Y, Nakagawa K et al (2024) Preoperative risk factors for ileostomy-associated kidney injury in colorectal tumor surgery following ileostomy formation. Int J Colorectal Dis 39(1):160
25. Bona D, Danelli P, Sozzi A, Sanzi M, Cayre L, Lombardo F et al (2023) C-reactive protein and procalcitonin levels to predict anastomotic leak after colorectal surgery: systematic review and meta-analysis. J Gastrointest Surg 27(1):166–179
26. Leourier P, Pellegrin A, Regimbeau JM, Sabbagh C (2023) Is early CT in cases of elevated postoperative CRP the best option for the diagnosis of colorectal anastomotic leakage? Int J Colorectal Dis 38(1):278
27. Daams F (2014) Prediction and diagnosis of colorectal anastomotic leakage: a systematic review of literature. World J Gastrointest Surg 6(2):14
28. Adamina M, Steffen T, Tarantino I, Beutner U, Schmied BM, Warschkow R (2015) Meta-analysis of the predictive value of C-reactive protein for infectious complications in abdominal surgery. Br J Surg 102(6):590–598
29. Tatsuoka T, Okuyama T, Takeshita E, Oi H, Noro T, Mitsui T et al (2021) Early detection of infectious complications using C-reactive protein and the procalcitonin levels after laparoscopic

colorectal resection: a prospective cohort study. Surg Today 51(3):397–403
30. McKechnie T, Cloutier Z, Archer V, Park L, Lee J, Heimann L et al (2024) Using preoperative C-reactive protein levels to predict anastomotic leaks and other complications after elective colorectal surgery: a systematic review and meta-analysis. Colorectal Dis 26(6):1114–1130
31. Chiarello MM, Fransvea P, Cariati M, Adams NJ, Bianchi V, Brisinda G (2022) Anastomotic leakage in colorectal cancer surgery. Surg Oncol 40
32. Hain E, Maggiori L, Manceau G, Mongin C, Prost à la Denise J, Panis Y (2017) Oncological impact of anastomotic leakage after laparoscopic mesorectal excision. Journal of British Surgery 3;104(3):288–95
33. Nakamura Y, Yamaura T, Kinjo Y, Kawase M, Kanto S, Kuroda N (2022) Impact of severe postoperative inflammatory response on recurrence after curative resection of colorectal cancer. Int J Colorectal Dis 37(11):2375–2386
34. Giaccaglia V, Salvi PF, Antonelli MS, Nigri G, Pirozzi F, Casagranda B et al (2016) Procalcitonin reveals early dehiscence in colorectal surgery. Ann Surg 263(5):967–972
35. Catarci M, Ruffo G, Borghi F, Patriti A, Delrio P, Scatizzi M et al (2020) Anastomotic leakage after elective colorectal surgery: a prospective multicentre observational study on use of the Dutch leakage score, serum procalcitonin and serum C-reactive protein for diagnosis. BJS Open 4(3):499–507
36. den Dulk M, Noter SL, Hendriks ER, Brouwers MAM, van der Vlies CH, Oostenbroek RJ et al (2009) Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. European Journal of Surgical Oncology (EJSO) 35(4):420–426

ARTICULO III

“Prognostic value of neutrophil-to-lymphocyte ratio at diagnosis in colorectal cancer: propensity score analysis”

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ORIGINAL PAPER

Prognostic value of neutrophil-to-lymphocyte ratio at diagnosis in colorectal cancer: propensity score analysis

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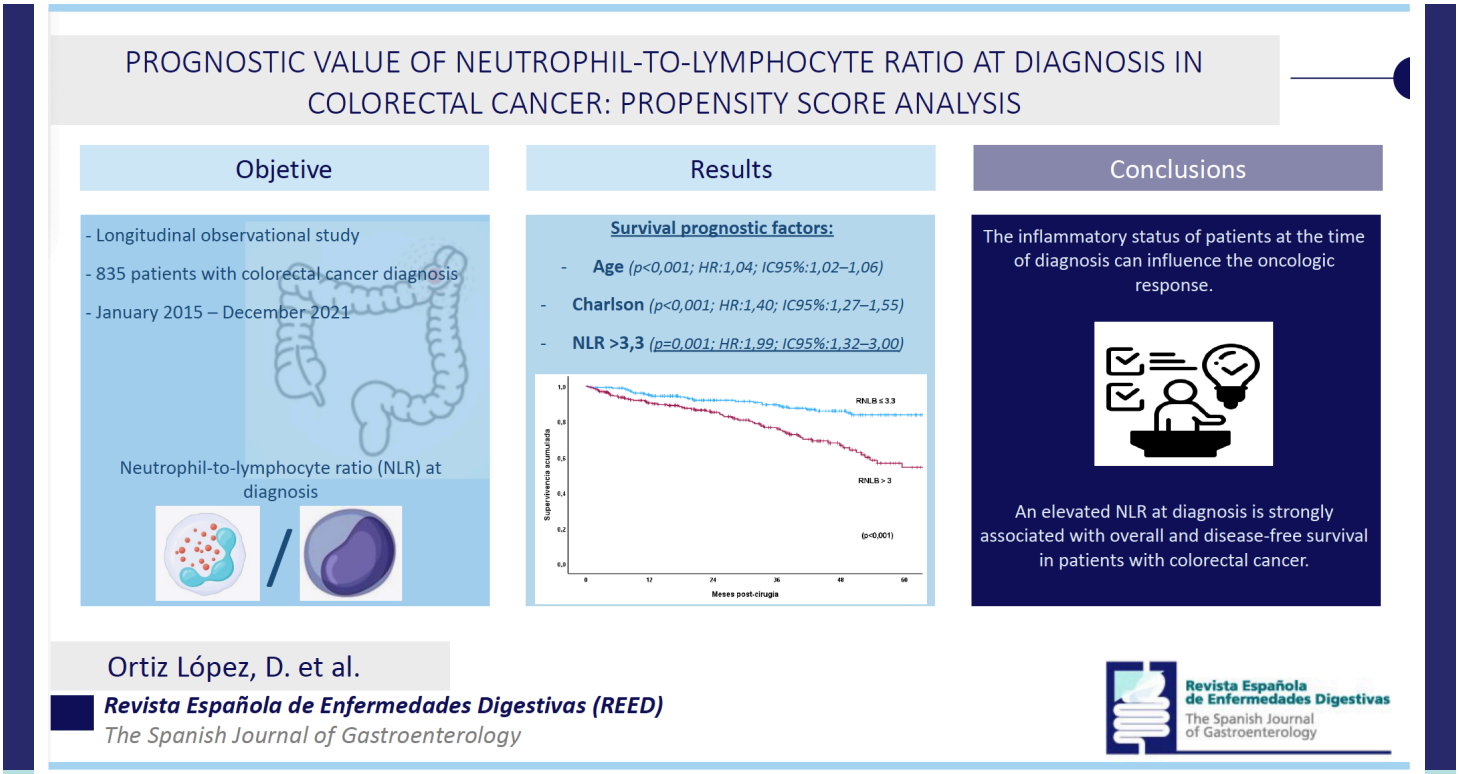

Lay summary

The neutrophil-to-lymphocyte ratio (NLR) is a parameter which is easily calculated using values from a complete blood count. It has been described in the literature that if elevated, it is associated with a proinflammatory state in the body. The main hypothesis of this study is that an elevated NLR is related to a worse prognosis, and therefore poorer survival, in patients diagnosed with colorectal cancer. To demonstrate this, a series of patients who underwent surgical intervention with a diagnosis of colorectal cancer from 2015 to 2021 was analysed. Among other data, we studied the NLR at the time of diagnosis. The patients were divided into two groups: one with a NLR > 3.3 and the other with a NLR ≤ 3.3. The two samples were homogenized to eliminate differences which might exist between the two populations, using what is called a propensity score analysis.
After conducting a statistical analysis of the factors influencing the prognosis of colorectal cancer, it was observed that a NLR > 3.3 at the time of diagnosis is an important prognostic factor for survival in these patients. Other factors related to survival include the patient's age and comorbidities. In conclusion, we find that an elevated baseline NLR (> 3.3) in patients with colorectal cancer at the time of diagnosis represents an adverse prognostic factor in terms of survival. Its use in routine practice could lead to the intensification of therapeutic strategies and post-treatment surveillance in these patients.

ABSTRACT

Introduction: baseline neutrophil-to-lymphocyte ratio (NLR) at the time of colorectal cancer (CRC) diagnosis has been proposed as a predictor of long-term survival. The aim of this study was to analyze its usefulness in a homogeneous population with control of the main confounding factors.

Methodology: observational study of 836 patients who underwent surgery for CRC. Patients were divided into two groups: NLR ≤ 3.3 *vs* NLR > 3.3. To control for confounders, they were matched one-to-one by propensity analysis. A final cohort of 526 patients was included in the study.

Results: the two groups were mismatched in terms of age, comorbidity, tumor stage, rectal location, and neoadjuvant therapy. Once matching was performed, baseline NLR was statistically significantly associated with long-term survival ($p < 0.001$) and behaved as an independent prognostic factor for survival ($p = 0.001$; HR: 1.99; 95 % CI: 1.32-3.00) when adjusted in a Cox regression model using age ($p < 0.001$; HR: 1.04; 95 % CI: 1.02-1.06) and the Charlson Comorbidity Index ($p < 0.001$; HR: 1.40; 95 % CI: 1.27-1.55). Neoadjuvant therapy lost its statistical significance ($p = 0.137$; HR: 1.59; 95 % CI: 0.86-2.93).

Conclusions: a high baseline NLR (> 3.3) in patients with colorectal cancer at diagnosis represents a poor prognostic factor in terms of survival. Its use in routine practice could intensify therapeutic strategies and follow-up in these patients.

Keywords: Colorectal cancer. Propensity analysis. Neutrophil-to-lymphocyte ratio. Survival.

INTRODUCTION

Colorectal cancer is the third most common cause of cancer-related death (1). Five-year survival reaches 90 % in early stages, while in metastatic stage, it does not exceed 15 % at five years (2). Identifying patients with a higher risk of recurrence and worse prognosis would allow for personalized treatment and the administration of more suitable targeted therapies. The tumor stage at diagnosis is the most important prognostic factor (3), but other factors such as tumor location (4), lymphovascular and/or perineural invasion (5), as well as certain genetic biomarkers (6) also influence prognosis. Postoperative complications, especially anastomotic dehiscence, are also a prognostic factor (7).

Authors´ contributions: Study design: D. O. L., J. M. G., and C. R. Q.; data collection: D. O. L., E. N. R., Y. S. Q., B. A. P., M. A. A., and J. G. G.; data analysis and interpretation: J. M. G., D. O. L., and C. R. Q.; writing: D. O. L., and J. M. G.; review and final approval: all authors.

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Ethical aspects: the study was approved by the hospital's Ethics and Clinical Research Committee (code 2020-279-1). All patients provided signed informed consent.

Conflict of interest: the authors declare no conflict of interest.

Artificial intelligence: the authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

Having a simple, inexpensive, and useful prognostic marker would help establish realistic expectations for the patient and their family. In this regard, since Virchow described the presence of neutrophils in tumor tissue in 1863 (8), it has been suggested that inflammation might not only play a role in carcinogenesis (9) but also in prognosis.

Systemic inflammatory status can be monitored using analytical parameters such as the neutrophil-to-lymphocyte ratio (NLR). Elevated NLR at diagnosis has proven to be a good prognostic factor in colorectal cancer (10) and another type of cancer (11,12).

However, while numerous studies support the predictive power of NLR (11,13-16), most are retrospective observational studies which do not adequately control for confounding factors. Moreover, the few studies which have homogenized the sample through propensity score matching (17,18) were performed with a relatively small number of patients.

The objective of our study was to analyze the prognostic value of the baseline NLR in a large sample of patients undergoing colorectal cancer surgery, where major confounding factors were controlled through propensity score matching.

METHODS

Design

This was a longitudinal observational study of an initial cohort of 836 patients that consecutively underwent surgery for colorectal cancer between January 2015 and December 2021 in our institution, with an average follow-up of 33 months. All patients that underwent elective surgery for colorectal cancer with curative intent were included, while those with complicated colorectal cancer requiring urgent surgery and those with incomplete postoperative histories or follow-up were excluded.

Patient management

Diagnosis was confirmed in all cases by a colonoscopy and a biopsy was performed by a gastroenterologist. As part of the staging process, all patients underwent blood tests with complete blood count and determination of tumor markers, a thoraco-abdominopelvic computed tomography (CT), and a pelvic magnetic resonance imaging for those diagnosed with rectal cancer. Preoperative evaluation was performed by a colorectal surgeon. Definitive staging followed the criteria of the American Joint Committee on Cancer (AJCC) staging system (8th edition) (19). Colon

Ortiz López D, Marchena Gómez J, Nogués Ramía E, Sosa Quesada Y, Arencibia Pérez B, Artiles Armas M, Gil García J, Roque Castellano C. Prognostic value of neutrophil-to-lymphocyte ratio at diagnosis in colorectal cancer: propensity score analysis. Rev Esp Enferm Dig 2024;116(8):408-415

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preparation was performed mechanically, and prophylactic oral and intravenous antibiotics were administered before surgery. Surgical procedures were performed by a colorectal surgery specialist, and anastomoses were created using mechanical suture devices.

The decision to administer neoadjuvant and/or adjuvant chemotherapy was based on the protocols of the hospital's Multidisciplinary Colorectal Tumor Committee. Data collection was performed via a prospectively maintained database.

Study variables

The main study variable was baseline NLR, and our initial hypothesis was that the baseline NLR is related to long-term survival in colorectal cancer patients. This parameter was obtained from the first complete blood count performed at the time of diagnosis, resulting from the neutrophil count to lymphocyte count ratio. The variable was then categorized into two groups, considering 3.3 as the cut-off value. This cut-off value was obtained based on the Youden index (20), which identified the NLR value with the highest sensitivity and specificity for predicting survival at the end of follow-up.

- Demographic data: age and sex
- Comorbidity: the Charlson Index was used, and was calculated preoperatively for each patient. It includes 19 comorbidities, scored 1, 2, 3, or 6 based on their presence or absence. The total score ranges from 0 to 37 points (21), where 0 indicates no comorbidity and > 4 points is considered as severe comorbidity.
- Tumor characteristics: the tumor location was categorized as either colon or rectal cancer based on the affected segment. The tumor stage was classified according to the 8th edition of the AJCC TNM staging system, including stages I, II, III, and IV (22). Additionally, several variables were collected, such as the number of isolated lymph nodes, the degree of differentiation (well/moderately differentiated *vs* poorly differentiated), the presence of lymphovascular and/or perineural invasion, and the status of surgical margins (free or involved).
- Type of surgery: surgical procedure performed, approach (open, laparoscopic, or robotic), and the need for conversion.
- Postoperative results: postoperative complications with special attention to anastomotic dehiscence, reoperations, operative mortality and days of postoperative stay. Postoperative complications were scored using the Comprehensive Complication Index (CCI) (23), similar to the Clavien-Dindo (24) classification but considering all complications, not just the most severe. The score ranges from 0 (no complications) to 100 points (death). Operative mortality was defined as deaths occurring within the first 90 days after surgery, or later if directly related to a postoperative complication.
- Chemotherapy: whether the patient received any kind of adjuvant or neoadjuvant therapy.

Outcome variable

The five-year cumulative survival was considered as the outcome variable. Survival time was defined as the period between surgery and the date of death or the last observation date if the patient was still alive. It was monitored through the patient's medical history or family contact.

Statistical analysis

Data were analyzed using the SPSS 29.0 statistical package for Windows (IBM Corporation, Armonk, NY, USA).

Descriptive analysis

Frequency and percentage were used to express categorical variable values. For numerical variables, the mean (± standard deviation) and/or median (interquartile range) were used depending on whether they followed a normal distribution. Kaplan-Meier survival curves were used to illustrate survival.

Univariate analysis

Initially, a comparative analysis was performed between the group of patients with NLR ≤ 3.3 and those with NLR > 3.3. The Chi-squared test was used to compare proportions, or Fisher's exact test if the conditions for the former were not met. To analyze differences between numerical variables, either the Student's t-test or the Mann-Whitney U test was applied based on whether the data followed a normal distribution or not. The log rank test was used to compare survival curves.

Propensity score analysis

In order to analyze the association between NLR and survival and obtain a more homogeneous sample, each case was matched with a similar control. This process was based on the propensity score, defined as the probability that each study participant would be assigned to each study arm (normal or elevated NLR) based on their baseline characteristics (covariates) (25). A logistic regression was used to obtain a propensity score for each patient, with the "outcome" variable being the categorized NLR. Covariates which were unbalanced between the two groups (NLR ≤ 3.3 *vs* NLR > 3.3) in the comparative analysis were introduced into the model.

Regarding matching, a one-to-one pair analysis without replacement was performed based on the estimated propensity score of each patient, using a caliper of 0.2 (26). The effectiveness of matching by propensity score was assessed using standardized mean differences before and after matching. Differences of < 0.10 support the assumption of balance between the two groups.

Finally, a Cox regression was performed to analyze the possible relationship between categorized NLR and long-term survival in the matched population. A significance level of $p < 0.05$ was considered, and the hazard ratio (HR) with a corresponding 95 % confidence interval (CI) was used as a measure of risk.

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RESULTS

Of the 836 patients initially included, 521 (62.3 %) were male and 315 (37.7 %) were female ($p < 0.001$), with a mean age of 68.7 years (SD ± 11.1). Table 1 describes the surgical procedures and approaches used.

The mean number of isolated lymph nodes in each surgical specimen was 24.8 (± 15.9). This variable was not included in the statistical analysis since the authors considered that the number of isolated nodes depended on uncontrollable factors such as the receipt of neoadjuvant treatment or the processing of surgical specimens by different specialists in Pathological Anatomy.

The mean baseline NLR was 3.2 (SD ± 2.6). After categorization, 572 patients (68.4 %) had a NLR ≤ 3.3, and 264 patients (31.6 %) had a NLR > 3.3. Operative mortality was 1 % (eight patients), including two cases of anastomotic dehiscence. The probability of being alive at one, three, and five years was 94.1 %, 85.7 %, and 73.0 %, respectively. At the end of the follow-up, 700 patients (83.7 %) were still alive, and 136 patients (16.3 %) had died.

Table 2 (left) shows the baseline characteristics of the unmatched sample based on whether they belonged to the NLR ≤ 3.3 group or the NLR > 3.3 group and the comparison between them according to different covariates. NLR was statistically significantly associated with long-term survival ($p < 0.001$). However, it was observed that there were disparities in age ($p < 0.001$), comorbidity ($p = 0.003$), stage ($p = 0.018$), rectal location ($p = 0.034$), and neoadjuvant treatment ($p < 0.001$). These covariates were used for matching.

Table 1. *Performed surgical procedures and approach*

Surgical procedure	*n* (%)
Right colectomy	305 (36.5 %)
Anterior rectal resection	214 (25.6 %)
Sigmoidectomy	174 (20.8 %)
Left colectomy	71 (8.5 %)
Segmental resection	33 (3.9 %)
Abdominoperineal amputation	19 (2.3 %)
Total colectomy	16 (1.9 %)
Miscellaneous	4 (0.5 %)
Approach	***n*** **(%)**
Laparoscopic surgery	492 (58.9 %)
Robotic surgery	73 (8.7 %)
Open surgery	271 (32.4 %)
Conversion	42 (7.9 %)

After a one-to-one propensity score matching without replacement, 263 patients remained in each group. Table 2 (right) presents the comparative analysis of these two matched groups. A slight imbalance persisted in the variables representing age ($p = 0.021$), comorbidity measured by the Charlson Index ($p = 0.012$), and neoadjuvant treatment ($p = 0.055$), but with standardized mean differences below 0.20, indicating a minimal effect on the balance between the two groups.

Baseline NLR after matching continued to be significantly associated with survival ($p < 0.001$) (Fig. 1). When adjusted using a Cox regression model (Fig. 2) for variables which were still unbalanced in the sample homogenized by the propensity score (age, comorbidity, and neoadjuvant treatment), baseline NLR remained an independent prognostic factor for survival ($p = 0.001$; HR: 1.99; 95 % CI: 1.32-3.00). Age ($p < 0.001$; HR: 1.04; 95 % CI: 1.02-1.06) and comorbidity (Charlson Index) ($p < 0.001$; HR: 1.40; 95 % CI: 1.27-1.55) retained their statistical significance, but not neoadjuvant treatment ($p = 0.137$; HR: 1.59; 95 % CI: 0.86-2.93).

DISCUSSION

The systemic inflammatory status at the time of cancer diagnosis is gaining importance. Systemic inflammation is believed to play a significant role in cancer response, correlating with prognosis (27). Proinflammatory systemic factors can act as initiators of carcinogenesis. In proinflammatory situations, macrophages and neutrophils in the area subjected to inflammatory stress release oxygen and nitrogen radicals which cause cellular damage to DNA, potentially initiating carcinogenesis (28). During neoplastic transformation, tumor cells release proinflammatory substances which contribute to creating a situation of systemic inflammation (29). A significant systemic inflammatory response would be associated with a worse prognosis in these patients (27).

In our study, after a propensity score matching, it was demonstrated that the inflammatory response measured by the NLR at the time of colorectal cancer diagnosis was related to long-term prognosis. Patients with a high NLR (> 3.3) had significantly lower survival rates than patients whose NLR was below this value.

Other analytical parameters have been used to measure systemic inflammation: platelet-to-lymphocyte ratio (30), lymphocyte-to-C-reactive protein (CRP) ratio (13), and CRP itself (31). These markers are economical and easy to obtain through routine blood tests. Undoubtedly, NLR has proven to be the most useful in relation to colorectal cancer (16).

Chiang et al. (32), in one of the longest series published, analyzed preoperative NLR in 3,857 patients with localized colorectal cancer (stages I-II-III) undergoing scheduled and urgent surgery. They concluded that an NLR > 3 was associated with worse disease-free survival of colorectal cancer, and this difference was more evident in colon cancer than in rectal cancer. Our study included stage IV patients treated with curative intent and excluded urgently operated patients.

Table 2. *Comparability of the two groups (NLR ≤ 3.3 vs NLR > 3.3) before and after matching according to the propensity score analysis*

	Total	Before matching (*n* = 836)				After matching (*n* = 526)			
		NLR ≤ 3.3 *n* (%) 572 (68.4)	NLR > 3.3 *n* (%) 264 (31.6)	*p*	SMD	NLR ≤ 3.3 *n* (%) 263 (50.0)	NLR > 3.3 *n* (%) 263 (50.0)	*p*	SMD
Age:									
Mean (± SD)	68.7 (± 11.1)	67.8 (± 10.6)	70.7 (± 11.9)	< 0.001	-0.258	68.7 (± 10.5)	70.7 (± 11.9)	0.021	-0.171
Median (IQR)	70 (62-77)	69.0 (61.3-75.0)	72.0 (64.0-79.0)			70.0 (63.0-76.0)	72.0 (64.0-79.0)		
Sex:									
Male	521 (62.3)	350 (61.2)	171 (64.8)	0.320	0.074	161 (61.2)	171 (65.0)	0.366	0.079
Female	315 (37.7)	222 (38.8)	93 (35.2)			102 (38.8)	92 (35.0)		
BMI:									
Mean (± SD)	26.9 (± 4.5)	27.01 (± 4.4)	26.6 (± 4.8)	0.117	0.099	27.0 (± 4.4)	26.6 (± 4.8)	0.254	0.091
Median (IQR)	27.0 (24.0-29.7)	27.0 (24.0-30.0)	26.0 (23.8-29.0)			27.0 (24.0-29.0)	26.0 (23.7-29.0)		
Charlson Index:									
Mean (± SD)	3.08 (± 2.2)	3.02 (± 1.49)	3.23 (± 1.49)	0.003	-0.142	3.0 (± 1.5)	3.2 (1.5)	0.012	-0.142
Median (IQR)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-4.0)			2.0 (2.0-4.0)	3.0 (2.0-4.0)		
Stage:									
I	229 (27.4)	167 (29.2)	62 (23.5)			83 (31.6)	62 (23.6)		
II	292 (34.9)	181 (31.6)	111 (42.0)	0.018	0.023	81 (30.8)	110 (41.8)	0.430	-0.076
III	258 (30.9)	187 (32.7)	71 (26.9)			84 (31.9)	71 (27.0)		
IV	57 (6.8)	37 (6.5)	20 (7.6)			15 (5.7)	20 (7.6)		
Grade:									
Differentiated	769 (92.0)	532 (92.8)	237 (90.1)	0.177	-0.101	246 (93.5)	237 (90.1)	0.152	-0.125
Undifferentiated	67 (8.0)	41 (7.2)	26 (9.9)			17 (6.5)	26 (9.9)		
Lymphovascular invasion:									
No	599 (71.7)	420 (73.3)	179 (68.1)	0.119	-0.116	194 (73.8)	179 (68.1)	0.150	-0.126
Yes	237 (298.3)	153 (26.7)	84 (31.9)			69 (26.2)	84 (31.9)		
Perineural invasion:									
No	660 (78.9)	457 (79.8)	203 (77.2)	0.397	-0.063	208 (79.1)	203 (77.2)	0.598	-0.046
Yes	176 (21.1)	116 (20.2)	60 (22.8)			55 (20.9)	60 (22.8)		
Resection margin:									
Free	816 (97.6)	560 (97.7)	256 (97.3)	0.730	-0.026	257 (97.7)	256 (97.3)	0.779	-0.024
Involved	20 (2.4)	13 (2.3)	7 (2.7)			6 (2.3)	7 (2.7)		

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Table 2 (Cont.). *Comparability of the two groups (NLR ≤ 3.3* vs *NLR > 3.3) before and after matching according to the propensity score analysis*

	Total	Before matching (*n* = 836)				After matching (*n* = 526)			
		NLR ≤ 3.3 *n* (%) 572 (68.4)	NLR > 3.3 *n* (%) 264 (31.6)	*p*	SMD	NLR ≤ 3.3 *n* (%) 263 (50.0)	NLR > 3.3 *n* (%) 263 (50.0)	*p*	SMD
Location:									
Colon	609 (72.8)	404 (70.6)	205 (77.7)	0.034	0.158	198 (75.3)	205 (77.9)	0.471	0.063
Rectum	227 (27.2)	168 (29.4)	59 (22.3)			657 (24.7)	58 (22.1)		
Anastomosis:									
No	39 (4.7)	29 (5.1)	10 (3.8)	0.414	-0.061	12 (4.6)	10 (3.8)	0.663	-0.038
Yes	797 (95.3)	543 (94.9)	254 (96.2)			251 (95.4)	253 (96.2)		
Neoadjuvant therapy:									
No	711 (85.0)	471 (82.3)	240 (90.9)	0.001	0.241	226 (85.9)	240 (91.3)	0.055	0.168
Yes	125 (15.0)	101 (17.7)	24 (9.1)			37 (14.1)	23 (8.7)		
Adjuvant therapy:									
No	455 (54.4)	309 (54.0)	146 (55.3)	0.729	0.026	150 (57.0)	146 (55.5)	0.725	-0.031
Yes	381 (45.6)	263 (46.0)	118 (44.7)			113 (43.0)	117 (44.5)		
Dehiscence:									
No	790 (94.5)	541 (94.6)	249 (94.3)	0.877	-0.011	250 (95.1)	248 (94.3)	0.698	-0.034
Yes	46 (5.5)	31 (5.4)	15 (5.7)			13 (4.9)	15 (5.7)		
Reintervention:									
No	755 (90.3)	514 (89.9)	241 (91.3)	0.517	0.048	238 (90.5)	240 (91.3)	0.762	0.026
Yes	81 (9.7)	58 (10.1)	23 (8.7)			25 (9.5)	23 (8.7)		
CCI:									
Mean (± DE)	10.8 (±19.0)	10.3 (±18.3)	11.9 (±20.3)	0.257	0.061	10.7 (±19.4)	12.0 (±20.3)	0.363	-0.063
Median (RIQ)	0.0 (0.0-20.9)	0.0 (0.0-20.9)	0.0 (0.0-20.9)			0.0 (0.0-20.9)	0.0 (0.0-20.9)		
Stay:									
Mean (± DE)	8.9 (± 7.6)	8.8 (± 7.6)	9.14 (± 7.5)	0.519	-0.043	8.7 (± 6.7)	9.2 (± 7.5)	0.820	-0.063
Median (RIQ)	6.0 (5.0-10.0)	6.0 (5.0-10.0)	6.0 (5.0-11.0)			6.0 (5.0-10.0)	6.0 (5.0-11.0)		
Operative mortality:									
No	828 (99.0)	568 (99.3)	260 (98.5)	0.270	0.084	259 (98.5)	259 (98.5)	1.000	0.000
Yes	8 (1.0)	4 (0.7)	4 (1.5)			4 (1.5)	4 (1.5)		
Survival mean (SE)* (months)	63.8 (0.95)	66.4 (0.95)	55.0 (2.00)	< 0.001	--	64.8 (1.5)	54.9 (2.0)	< 0.001	--
Five-year cumulative survival (SE)	73.0 % (0.02)	80.5 % (0.03)	54.5 % (0.05)			76.2 % (0.04)	54.2 % (0.05)		

SD: standard deviation; BMI: body mass index; SMD: standardized mean difference; IQR: interquartile range; SE: standard error; CCI: Comprehensive Complication Index. *Median survival not available due to the high prevalence of censored patients at the end of the follow-up.

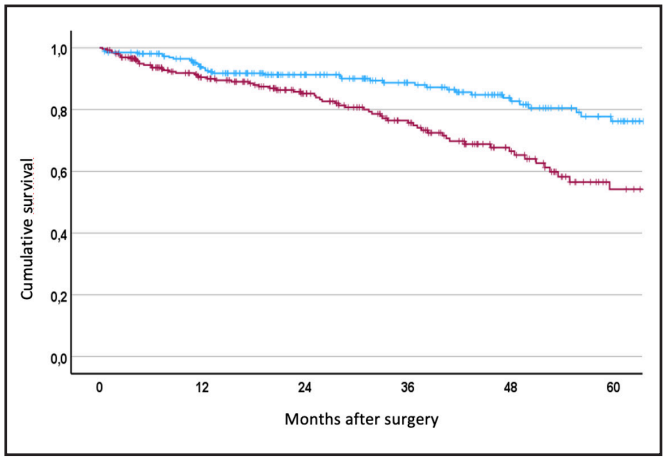

Fig. 1. *Survival curves for patients with baseline neutrophil-to-lymphocyte ratio (NLR) ≤ 3.3 (blue) and patients with baseline NLR > 3.3 (red) (p < 0.001).*

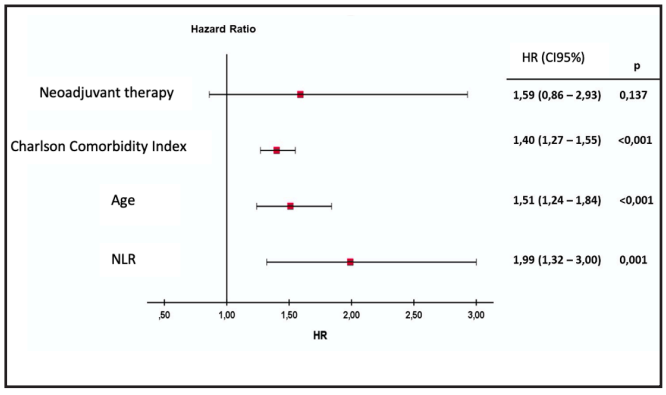

Fig. 2. *Forest plot of the multivariate analysis (Cox regression) of survival in patients with colorectal cancer after adjusting baseline neutrophil-to-lymphocyte ratio (NLR) for age, comorbidity measured by the Charlson Index, and neoadjuvant therapy.*

Although colon cancer and rectal cancer are different entities for many authors, we did not conduct a separate study since this variable was perfectly balanced in the study population after matching. Similarly, we decided not to include urgently operated patients since, in stressful situations, urgency itself could alter the proinflammatory state of the body, interfering with the NLR result and affecting the assessment of the inflammatory state due to neoplasm. For the same reason, NLR determination was performed before initiating any surgical or chemotherapeutic treatment.

The NLR cut-off point beyond which it should be considered pathological has been debated. Forget et al. (33), in a public health study, set the upper limit of normality at the value of 3.53. However, there is no consensus in the literature. Our cut-off level of 3.3 was obtained, as in several published studies, from our data using a ROC curve and the Youden index (20). Other authors have set indicative cut-off values for poor prognosis at NLR > 2.72 (34) or even > 5 (14,15).

Limitations of this study include the single-center and retrospective study design, although data collection was prospectively performed. Genetic tumor biomarkers were not considered since they were determined in very few patients (metastatic or suggestive of BRAF mutation). Regarding its strengths, it should be highlighted that the analytical determination from which the baseline NLR was collected was performed under the most basal conditions to avoid biases induced by an inflammatory state different from that caused by the tumor. Additionally, the homogeneity of our sample obtained through propensity score matching, controlling for possible confounding biases, and the large number of patients studied, should also be emphasized.

CONCLUSIONS

An elevated baseline NLR (> 3.3) in patients with colorectal cancer at the time of diagnosis represents a poor prognostic factor in terms of survival. It is a simple and inexpensive parameter to determine. Its use in routine practice could intensify therapeutic strategies and follow-up in these patients.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. DOI: 10.3322/caac.21660
2. Naszai M, Kurjan A, Maughan TS. The prognostic utility of pre-treatment neutrophil-to-lymphocyte-ratio (NLR) in colorectal cancer: a systematic review and meta-analysis. Cancer Med 2021;10:5983-97. DOI: 10.1002/cam4.4143
3. Van den Berg I, Coebergh van den Braak RRJ, Van Vugt JLA, et al. Actual survival after resection of primary colorectal cancer: results from a prospective multicenter study. World J Surg Oncol 2021;19(1):96. DOI: 10.1186/s12957-021-02207-4
4. Yahagi M, Okabayashi K, Hasegawa H, et al. The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. J Gastrointest Surg 2016;20:648-55. DOI: 10.1007/s11605-015-3026-6
5. Skancke M, Arnott SM, Amdur RL, et al. Lymphovascular invasion and perineural invasion negatively impact overall survival for stage II adenocarcinoma of the colon. Dis Colon Rectum 2019;62:181-8. DOI: 10.1097/DCR.0000000000001258
6. Puerta-García E, Canadas-Garre M, Calleja-Hernández MA. Molecular biomarkers in colorectal carcinoma. Pharmacogenomics 2015;16:1189-222. DOI: 10.2217/PGS.15.63
7. Ortiz-López D, Marchena-Gómez J, Nogués-Ramía E, et al. Utility of a new prognostic score based on the Comprehensive Complication Index (CCI®) in patients operated on for colorectal cancer (S-CRC-PC score). Surg Oncol 2022;42:101780. DOI: 10.1016/j.suronc.2022.101780
8. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet (London, England) 2001;357(9255):539-45. DOI: 10.1016/S0140-6736(00)04046-0
9. Yashiro M. Ulcerative colitis-associated colorectal cancer. World J Gastroenterol 2014;20:16389-97. DOI: 10.3748/wjg.v20.i44.16389
10. Li M-X, Liu X-M, Zhang X-F, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 2014;134:2403-13. DOI: 10.1002/ijc.28536

11. Yu Y, Wang H, Yan A, et al. Pretreatment neutrophil to lymphocyte ratio in determining the prognosis of head and neck cancer: a meta-analysis. BMC Cancer 2018;18. DOI: 10.1186/s12885-018-4230-z

12. Mjaess G, Chebel R, Karam A, et al. Prognostic role of neutrophil-to-lymphocyte ratio (NLR) in urological tumors: an umbrella review of evidence from systematic reviews and meta-analyses. Acta Oncol (Madr) 2021;60. DOI: 10.1080/0284186X.2021.1886323

13. He X, Su A, Xu Y, et al. Prognostic role of lymphocyte-C-reactive protein ratio in colorectal cancer: a systematic review and meta-analysis. Front Oncol 2022;12:905144. DOI: 10.3389/fonc.2022.905144

14. Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev 2017;58:1-13. DOI: 10.1016/j.ctrv.2017.05.005

15. Haram A, Boland MR, Kelly ME, et al. The prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review. J Surg Oncol 2017;115:470-9. DOI: 10.1002/jso.24523

16. Naszai M, Kurjan A, Maughan TS. The prognostic utility of pre-treatment neutrophil-to-lymphocyte-ratio (NLR) in colorectal cancer: a systematic review and meta-analysis. Cancer Med 2021;10:5983-97. DOI: 10.1002/cam4.4143

17. Balde AI, Fang S, He L, et al. Propensity score analysis of recurrence for neutrophil-to-lymphocyte ratio in colorectal cancer. J Surg Res 2017;219:244-52. DOI: 10.1016/j.jss.2017.05.109

18. Mazaki J, Katsumata K, Kasahara K, et al. Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: a propensity score analysis. BMC Cancer 2020;20. DOI: 10.1186/s12885-020-07429-5

19. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9. DOI: 10.3322/caac.21388

20. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32-5. DOI: 10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0.CO;2-3

21. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245-51. DOI: 10.1016/0895-4356(94)90129-5

22. Weiser MR. AJCC 8th Edition: Colorectal Cancer. Ann Surg Oncol 2018;25:1454-5. DOI: 10.1245/s10434-018-6462-1

23. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1-7. DOI: 10.1097/SLA.0b013e318296c732

24. 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;240:205-13. DOI: 10.1097/01.sla.0000133083.54934.ae

25. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424. DOI: 10.1080/00273171.2011.568786

26. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150-61. DOI: 10.1002/pst.433

27. Bai Z, Zhou Y, Ye Z, et al. Tumor-infiltrating lymphocytes in colorectal cancer: the fundamental indication and application on immunotherapy. Front Immunol 2022;12. DOI: 10.3389/fimmu.2021.808964

28. Schmitt M, Greten FR. The inflammatory pathogenesis of colorectal cancer. Nat Rev Immunol 2021;21:653-67. DOI: 10.1038/s41577-021-00534-x

29. Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: underlying factors, effects, and prognostic significance. World J Gastroenterol 2019;25:4383-404. DOI: 10.3748/wjg.v25.i31.4383

30. Gui W, Wang X, Luo Y, et al. Platelet to lymphocyte ratio as a prognostic factor in patients with advanced colorectal cancer undergoing palliative treatment. Ann Palliat Med 2020;9. DOI: 10.21037/apm-20-1389

31. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci 2011;48:155-70. DOI: 10.3109/10408363.2011.599831

32. Chiang SF, Hung HY, Tang R, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis 2012;27(10):1347-57. DOI: 10.1007/s00384-012-1459-x

33. Forget P, Khalifa C, Defour JP, et al. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes 2017;10(1):12. DOI: 10.1186/s13104-016-2335-5

34. Li Y, Jia H, Yu W, et al. Nomograms for predicting prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. Int J Cancer 2016;139:220-31. DOI: 10.1002/ijc.30071

ARTICULO IV

“Prognostic impact of persistent postoperative neutrophil-to-lymphocyte ratio elevation one year after colorectal cancer surgery”

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ORIGINAL ARTICLE

Prognostic impact of persistent postoperative neutrophil-to-lymphocyte ratio elevation 1 year after colorectal cancer surgery

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Abstract
Colorectal cancer (CRC) remains a major cause of cancer-related mortality despite advances in screening and treatment. Inflammation plays a key role in tumor progression, with the neutrophil-to-lymphocyte ratio (NLR) emerging as a potential prognostic marker. While preoperative NLR is a well-established predictor of survival, its prognostic value 1 year postoperatively remains underexplored. This study aims to evaluate the prognostic significance of NLR 1 year after curative CRC surgery, identify factors associated with its elevation, and assess its impact on survival and recurrence. A retrospective analysis was conducted on 788 patients who underwent curative-intent CRC surgery between 2015 and 2022. NLR was assessed preoperatively and 1 year postoperatively, using a cutoff of 3.3. Patients were categorized into four subgroups: "Low-Low": NLR ≤ 3.3 pre- and postoperatively; "Low–High": NLR ≤ 3.3 preoperatively but > 3.3 postoperatively; "High-Low": NLR > 3.3 preoperatively but ≤ 3.3 postoperatively, and "High-High": NLR > 3.3 at both time points. Survival analysis was performed using Cox regression. Postoperative NLR values were significantly lower than preoperative levels (median: 2.8 vs. 4.1, $p < 0.001$). An elevated post-NLR (> 3.3) correlated with poorer survival and higher recurrence rates. The "Low–High" group exhibited the worst prognosis, with a 5-year survival rate of 42.6% compared to 79.8% in the "Low-Low" group. Multivariate analysis confirmed post-NLR > 3.3 as an independent predictor of worse survival (HR: 3.49; 95%CI 2.41–5.04). Persistently elevated NLR 1 year after CRC surgery is associated with worse survival and higher recurrence. Routine postoperative NLR monitoring may help identify high-risk patients for closer follow-up and early intervention.

Keywords Colorectal cancer · Inflammatory status · Neutrophil-to-lymphocyte ratio · Overall survival · Disease-free survival

Introduction

Despite advancements in screening and therapeutic strategies, colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide. In the United States, CRC is the third most frequently diagnosed malignancy and the second leading cause of cancer-related death overall. Notably, it is the primary cause of cancer mortality in men under 50 years of age [1]. It has been reported that the mean number of years of potential life lost by colorectal cancer may exceed 15 years [2].

It is well known that tumor stage, high levels of serum Carcinoembryonic antigen (CEA), and carbohydrate-antigen 19–9 (CA 19.9) tumor markers, as well as certain genetic biomarkers [3] are good predictors of survival. There is also increasing evidence, suggesting that systemic inflammation is closely related to the pathogenesis, growth, and metastatic potential of CRC [4–6]. This is why in recent years, a series of inflammatory markers [7] have been added as predictors of poor outcome in CRC patients. Of these, the best known and most valued is the Neutrophil-To-Lymphocyte ratio (NLR) [8]. Several studies employing propensity score analysis [9, 10], as well as a series of published meta-analyses and systematic reviews [11–15], have demonstrated an

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association between elevated preoperative NLR and patient survival in CRC.

However, the progression of the inflammatory state following curative surgery for colorectal cancer and its prognostic implications remain less extensively studied. It is not yet clearly established how inflammatory markers evolve postoperatively—whether they decrease, increase, or remain stable. The long-term outcomes associated with persistently elevated NLR after surgery also remain poorly understood. Furthermore, it is unclear what occurs in patients whose inflammatory markers were initially within normal ranges but become elevated after 1 year of follow-up. While some studies have investigated this issue, their findings have been inconsistent.

This study aimed to assess the characteristics and prognostic implications of patients with elevated NLR 1 year after they underwent surgery for colorectal cancer. Additionally, to determine the factors influencing NLR elevation and to evaluate the implications of postoperative changes in this marker. We hypothesized that the persistence of an elevated NLR is a sign of poor prognosis in patients operated on for CRC with curative intent.

Methods

Study design and participants

This is an observational, longitudinal study from a cohort of 935 patients consecutively operated on for colorectal cancer between 2015 and 2022 at our institution. The setting was a tertiary referral center that serves a population of approximately 400,000 inhabitants.

Inclusion criteria patients diagnosed with colorectal cancer undergoing elective surgery with curative intent who had survived at least 1 year after surgery and had undergone a blood test at 1 year, including a full blood count. All included stage IV cases met strict criteria for curative resection, defined as complete removal of the primary tumor and all detectable metastatic lesions.

Exclusion criteria patients with colorectal cancer in whom palliative surgery was performed, patients with complicated colorectal cancer requiring urgent surgery, and those with incomplete postoperative histories and/or follow-up. The number and characteristics of the excluded patients were not collected.

The study was approved by the center's Clinical Research and Ethics Committee (code: 2020-279-1).

Management of the patient

A colorectal surgeon initially evaluated patients. The preoperative diagnosis of colorectal cancer was consistently established through colonoscopy and biopsy. Staging studies included thoraco-abdomino-pelvic CT scans and/or pelvic MRI, routine blood tests, tumor markers CEA and CA 19.9, and additional investigations as required based on the patient's underlying condition. All patients underwent mechanical bowel preparation and received antibiotic prophylaxis, orally and intravenously, before surgery. Surgical procedures were performed by a specialist colorectal surgeon.

Definitive postoperative diagnosis was based on histological examination of the resected specimen, following the criteria outlined in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system[16].

The decision to administer neoadjuvant and/or adjuvant chemotherapy was guided by the protocols established by the hospital's Multidisciplinary Colorectal Tumor Board. Patients with rectal cancer classified as T3 or T4 and/or with lymph-node involvement received neoadjuvant chemoradiotherapy. Similarly, patients with stage IV colorectal cancer deemed potentially curable also underwent neoadjuvant chemotherapy. Patients with high-risk stage II and stage III colon cancer were offered standard adjuvant chemotherapy. Stage IV patients included in the study were all treated with curative intent: resection of the primary tumor and removal of metastases.

Follow-up

Follow-up was conducted through blood tests including tumor markers every three months for the first two years, then every 6 months up to 5 years. Additionally, an annual thoraco-abdominal CT scan was performed, along with a colonoscopy at 1 year and 4 years post-surgery. Neoplasm recurrence was defined as the detection of a local recurrence on endoscopy or the presence of regional or distant metastasis on radiologic studies and/or reoperation.

Data collection and definitions

Data were collected from a database in which patients were prospectively included. The following variables were analyzed:

Demographic and clinical data

Age, sex, body mass index (BMI), and comorbidity measured by the Charlson Comorbidity Index (CCI) were recorded. The CCI was calculated preoperatively for each patient and includes 19 comorbidities, each assigned a weight of 1, 2, 3, or 6 based on their presence or absence. The total score ranges from 0 to 37 points [17]. A score of 0 typically indicates no comorbidity, while scores > 4 are considered indicative of severe comorbidity.

Data laboratory

The baseline NLR was calculated from a blood sample obtained immediately before surgery. The postoperative NLR (Post-NLR) was derived from a blood sample taken 1 year after surgery in patients who could complete this follow-up period.

The NLR was calculated using the formula: absolute neutrophil count (number/μL) /absolute lymphocyte count (number/μL). High NLR values were considered to reflect a high inflammatory state.

NLR was analyzed both as a continuous variable and as a categorical variable. A cut-off value of 3.3 was applied, as determined by the Youden index [18] from a previous study on the same patient cohort [9]. This index identified the NLR value with the highest sensitivity and specificity on the ROC curve for predicting patient survival. The cutpoints were "≤ 3.3" for "low NLR" and > 3.3 for "high NLR".

Tumor localization and histopathological features

Tumor localization was categorized as colon cancer or rectal cancer based on the affected segment. Tumor staging was determined using the final histopathological report of the resected specimen and classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system[16] (ypTNM) into stages I, II, III, and IV. Additionally, the presence of lymphovascular and/or perineural invasion was collected.

Surgical data

Surgical procedure, surgical approach, postoperative complications according to Clavien–Dindo classification [19], and operative mortality were recorded. Operative mortality was defined as any death occurring within 30 days of surgery or any subsequent death that was determined to be a direct consequence of a postoperative complication. The variable Clavien–Dindo classification was categorized as no complications (grade 0) vs minor complications (grades I–II) vs severe complications (grades III–V).

Neo and/or adjuvant therapy

It was recorded whether patients had received neoadjuvant chemotherapy and/or radiotherapy or adjuvant chemotherapy.

Study groups

First, the sample was divided into two major groups according to post-NLR levels: patients with post-NLR ≤ 3.3 and patients with post-NLR > 3.3. Similarly, to assess the significance of the changes in NLR between the preoperative and 1-year postoperative values, patients were divided into 4 subgroups according to the evolution of the observed NLR values [20–22]:

(I) Normal group: pre- and postoperatively low inflammatory state (baseline NLR ≤ 3.3/post-NLR ≤ 3.3). Low preoperative values to low postoperative values *(low–low)*.
(II) Normalized group: preoperatively high but postoperatively low inflammatory state (baseline NLR > 3.3/post-NLR ≤ 3.3). High preoperative values to low postoperative values *(high–low)*.
(III) Exacerbation group: preoperatively low inflammatory state but postoperatively high inflammatory state (baseline NLR ≤ 3.3/post-NLR > 3.3). Low preoperative values to high postoperative values *(low–high)*.
(IV) Elevated group: persistently high inflammatory state (baseline NLR > 3.3/post-NLR > 3.3). High preoperative values to high postoperative values *(high–high)*.

Output measures

NLR 1 year after surgery (post-NLR), global survival time, and disease-free survival time were the output variables. Survival time was defined as the interval from the curative resection to death or censoring. Disease-free survival time was defined as the period between surgery and the detection of tumor recurrence.

Statistical analysis

Data analysis was performed using the statistical software package SPSS version 29.0 for Windows (IBM Corporation, Armonk, NY, USA). Graphics were performed using the software Jamovi version 2.3 (The Jamovi Project, 2022).

Descriptive analysis

Categorical variables were expressed as frequencies and percentages. Numerical variables were reported as mean ($\pm$ standard deviation) and/or median (interquartile range), depending on whether or not they followed a normal distribution. Kaplan–Meier method was used to construct survival curves.

Univariate analysis

First, we assessed whether there were significant differences between the values of baseline NLR and post-NLR. For this purpose, we employed the Wilcoxon test, a non-parametric

statistical method designed for the comparison of two related samples.

A univariate analysis was then performed analyzing possible differences between patients with a high postoperative inflammatory status (post-NLR > 3.3) and patients with a low postoperative inflammatory status (post-NLR ≤ 3.3) concerning a series of predictor variables. This analysis allowed us to know which factors were related to postoperative NLR elevation and which variables could behave as confounding factors in the multivariate analysis of survival. Proportions were compared using the Chi-squared test when applicable or Fisher's exact test when not. For numerical variables, the Student's t test or Mann–Whitney U test was employed, depending on whether or not the data followed a normal distribution.

Survival analysis

The log-rank test was used to compare the survival curves of patients with high and low postoperative inflammatory status. Likewise, it was employed to compare the survival curves of the four subgroups classified according to the changes in their preoperative and postoperative NLR levels.

Multivariate analysis

A Cox regression model was performed to identify independent risk factors for long-term survival after 1 year of surgery in patients with elevated post-NLR. Predictor variables included post-NLR adjusted for all those variables that were statistically significant and clinically relevant in the univariate analysis comparing the two groups (post-NLR ≤ 3.3 vs. post-NLR > 3.3).

A p value < 0.05 was considered statistically significant. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated for significant variable associations.

Results

Patient characteristics

Of the initial 935 patients, 788 patients met the complete inclusion criteria. All of them were followed up at least 1 year after surgery, with a mean follow-up after surgery of 4.2 years. Fifty-two patients had died during the first year of follow-up. Operative mortality was 1% (9 patients). In addition to 30-day mortality, we observed 3 additional deaths between 30 and 90 days postoperatively, totaling a 90-day mortality rate of 1.3%. The remaining cases did not reach 1 year of follow-up, did not have a blood sample determination 1 year after surgery, or had an acute episode of intercurrent pathology at that time that could alter the neutrophil–lymphocyte ratio.

Among the 788 patients included in the final study sample, 483 (61.3%) were men and 305 (38.7%) women ($p < 0.001$), median age 69 years (IQR: 62.0–76.0).

The tumor was located in the colon in 554 (70.3%) patients and in the rectum in 234 (29.7%) patients. There were 272 (34.5%) right colectomies, 64 (8.1%) left colectomies, 171 (21.7%) sigmoidectomies, 212 (26.9%) anterior rectal resections, 29 (3.7%) segmental resections, 7 (0.9%) combined resections, 20 (2.5%) abdominoperineal amputations, and 13 (1.6%) total colectomies. Regarding the surgical approach, 218 (27.7%) patients underwent open surgery, 471 (59.8%) underwent laparoscopic surgery, and 99 (12.6%) underwent robotic surgery. According to the Clavien–Dindo classification, 149 (18.9%) patients experienced minor complications, while 102 (12.9%) suffered severe complications. Anastomotic leakage was recorded in 42 (5.3%) cases. Neoadjuvant therapy was administered predominantly in rectal cancer cases. A minority of colon cancer patients with potentially resectable metastases also received neoadjuvant chemotherapy (7 patients).

During follow-up from the first year after surgery, 122 (15.5%) patients died, while 666 (84.5%) remained alive. At the same time, 139 (17.6%) recurrences were diagnosed during the follow-up of this sample of patients.

The remaining baseline characteristics of the sample are detailed in the left column of Table 2.

Differences between baseline NLR and post-NLR

The median baseline NLR was 2.58 (IQR: 1.80–3.63), and the median post-NLR was 1.84 (IQR: 1.30–2.72). These differences were statistically significant ($p < 0.001$) (Fig. 1). Regarding the established cut-off point 3.30, 251 patients (31.9%) had an elevated NLR preoperatively, and 131 (16.6%) patients maintained elevated NLR postoperatively. These differences were also significant ($p < 0.001$).

Regarding the four subgroups, Table 1 presents the frequencies of the various possible combinations according to the pre- and post-NLR values. Most patients (59.4%) exhibited low NLR levels before and after surgery. Regarding tumor stage, a linear association was observed between NLR subgroups and TNM stage ($p = 0.028$), with subgroups exhibiting elevated post-NLR values more frequently presenting with advanced-stage disease (Fig. 2). Stage IV patients were distributed across the four NLR subgroups, with the majority falling into the high–high group.

Relationship of pre- and post-NLR with recurrence and survival

Both baseline NLR ($p = 0.005$; HR: 1.09, CI95%: 1.03–1.16) and post-NLR ($p < 0.001$; HR: 1.28, CI95%: 1.21–1.37) were

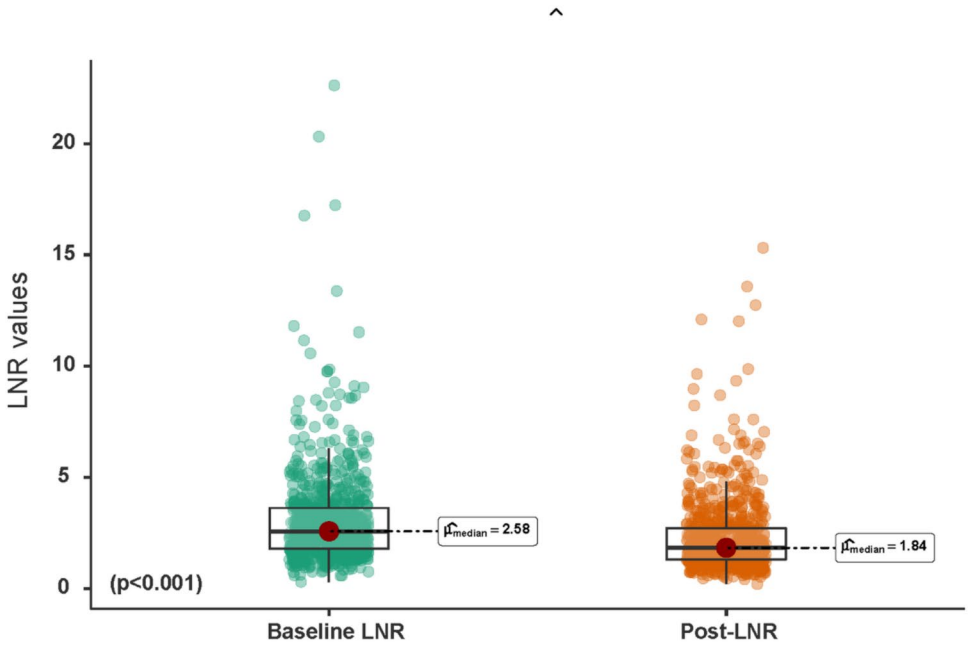

Fig. 1 Differences observed between baseline NLR and post-NLR (1 year after surgery) as continuous variables ($p < 0.001$) (Wilcoxon test)

Table 1 Frequency distribution of the different subgroups according to changes observed between preoperative and postoperative NLR values

Subgroups (pre-NLR/post-NLR)	Baseline NLR	Post-NLR	n (%)	TNM stage by subgroups n (%)
Normal: pre-NLR ≤ 3.3/post-NLR ≤ 3.3	Low	Low	468 (59.4)	I: 111 (23.7) II: 156 (33.3) III: 172 (36.8) IV: 29 (6.2)
Normalized: pre-NLR > 3.3/post-NLR ≤ 3.3	High	Low	189 (24.0)	I: 41 (21.7) II: 84 (44.4) III: 53 (28.0) IV: 11 (5.8)
Exacerbated: pre-NLR ≤ 3.3/post-NLR > 3.3	Low	High	62 (7.9)	I: 11 (17.7) II: 21 (33.9) III: 23 (37.1) IV: 7 (11.3)
Elevated: pre-NLR > 3.3/post-NLR > 3.3	High	High	69 (8.8)	I: 11 (15.9) II: 20 (29.0) III: 29 (42.0) IV: 9 (13.0)

significantly associated with long-term survival. At the end of follow-up, 580 (88.3%) of patients with post-NLR ≤ 3.3 and 86 (65.6%) of patients with post-NLR > 3.3 were alive. These differences were statistically significant ($p < 0.001$; OR: 3.94, 95%CI: 2.56–6.10).

In terms of survival, patients with post-NLR ≤ 3.3 had a mean survival of 88.5 months (95%CI 86.3–90.6) while patients with post-NLR > 3.3 had a mean survival of 68.7 months (95CI 62.5–74.9) (Fig. 3). Because of the number of censored cases, median survival could not be calculated. Among patients with post-NLR ≤ 3.3, the probability of being alive at 1, 3, and 5 years was 99.7%, 93.8%, and 85.7%, respectively. In patients with post-NLR > 3.3, the probability of being alive at 1, 3, and 5 years was 99.2%, 77.4%, and 62.7%, respectively. These differences were statistically significant ($p < 0.001$; HR: 3.49, 95%CI 2.41–5.04).

Similarly, recurrence rates were significantly higher in patients with post-NLR > 3.3 (38.2%) compared to those with post-NLR ≤ 3.3 (13.5%) ($p < 0.001$; HR: 3.84, 95%CI 2.65–5.56) (Fig. 4).

When stratifying by NLR evolution, we observed significant differences between the 4 subgroups ($p < 0.001$) (Fig. 5). Patients with an NLR ≤ 3.3 who still had a low NLR 1 year after surgery had the best prognosis, with a probability of being alive at 5 years of 88.3%. In contrast, patients with a preoperative NLR ≤ 3.3 who 1 year after surgery had

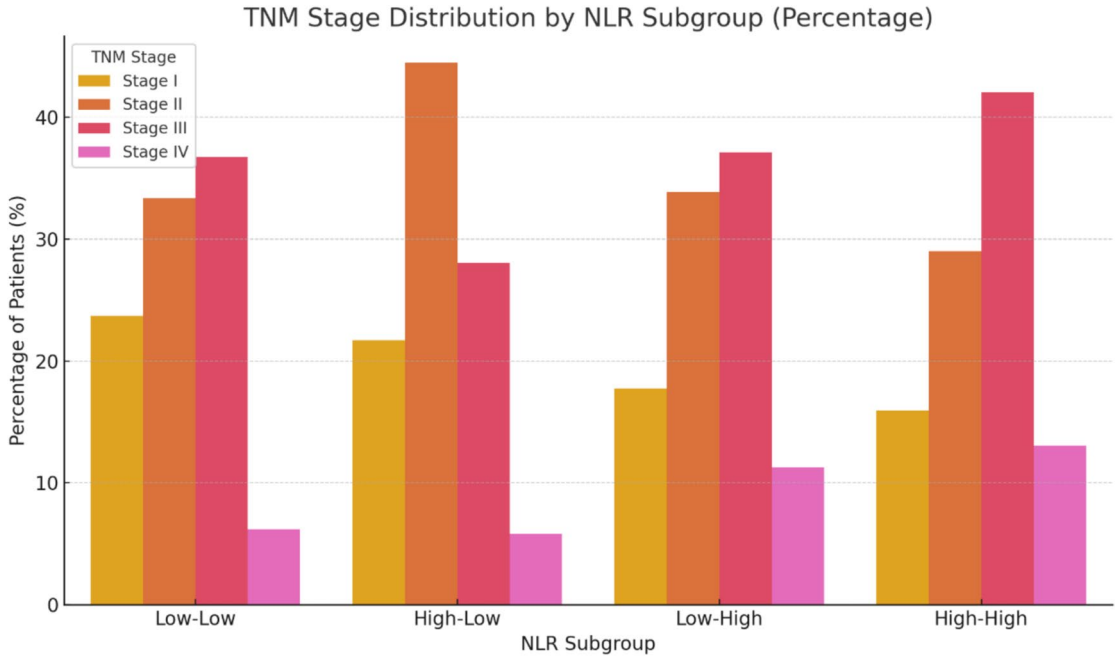

Fig. 2 Distribution of TNM stages across postoperative NLR subgroups. A linear association was observed between subgroup classification and tumor stage ($p = 0.028$), with higher post-NLR values associated with more advanced disease stages

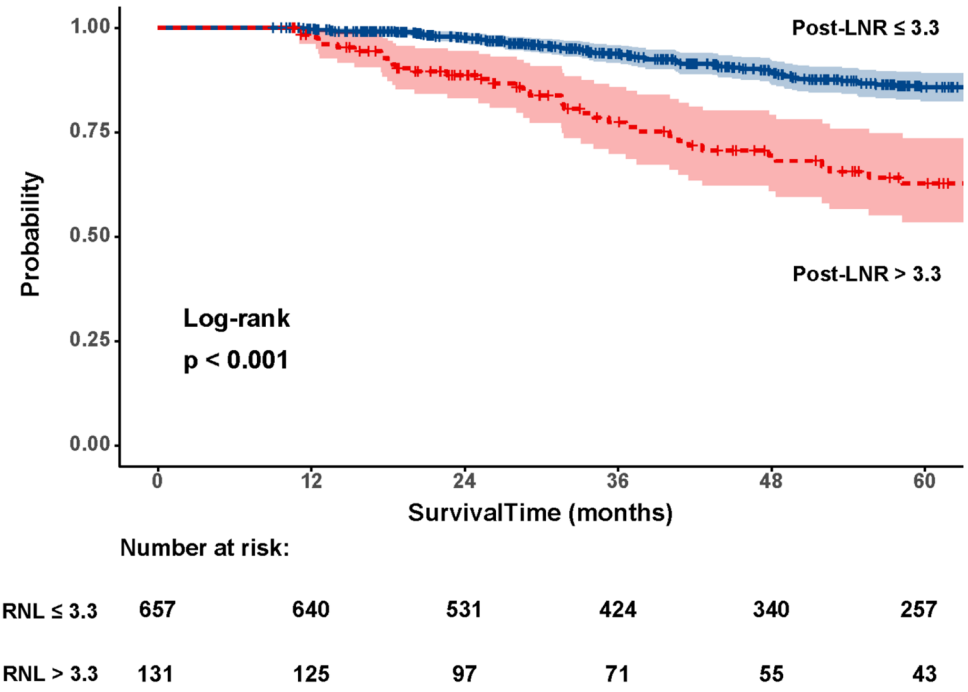

Fig. 3 Actuarial Kaplan–Meier survival analysis for patients with post-NLR ≤ 3.3 versus post-NLR > 3 (p < 0.001). Log-Rank test

NLR values > 3.3 had a worse prognosis, with a probability of being alive at 5 years of only 54.9%.

Factors associated with NLR at 1 year after surgery

Table 2 shows the variables that were associated with NLR values at 1 year after surgery and that could act as confounders in the analysis of survival. We highlight the comorbidity measured by the Charlson Index ($p < 0.001$; OR:1.25, 95%CI 1.11–1.40), the baseline NLR values both as a continuous variable ($p < 0.001$; OR: 1.27; 95%CI 1.16–1.39) and as a categorical variable ($p < 0.001$; OR:

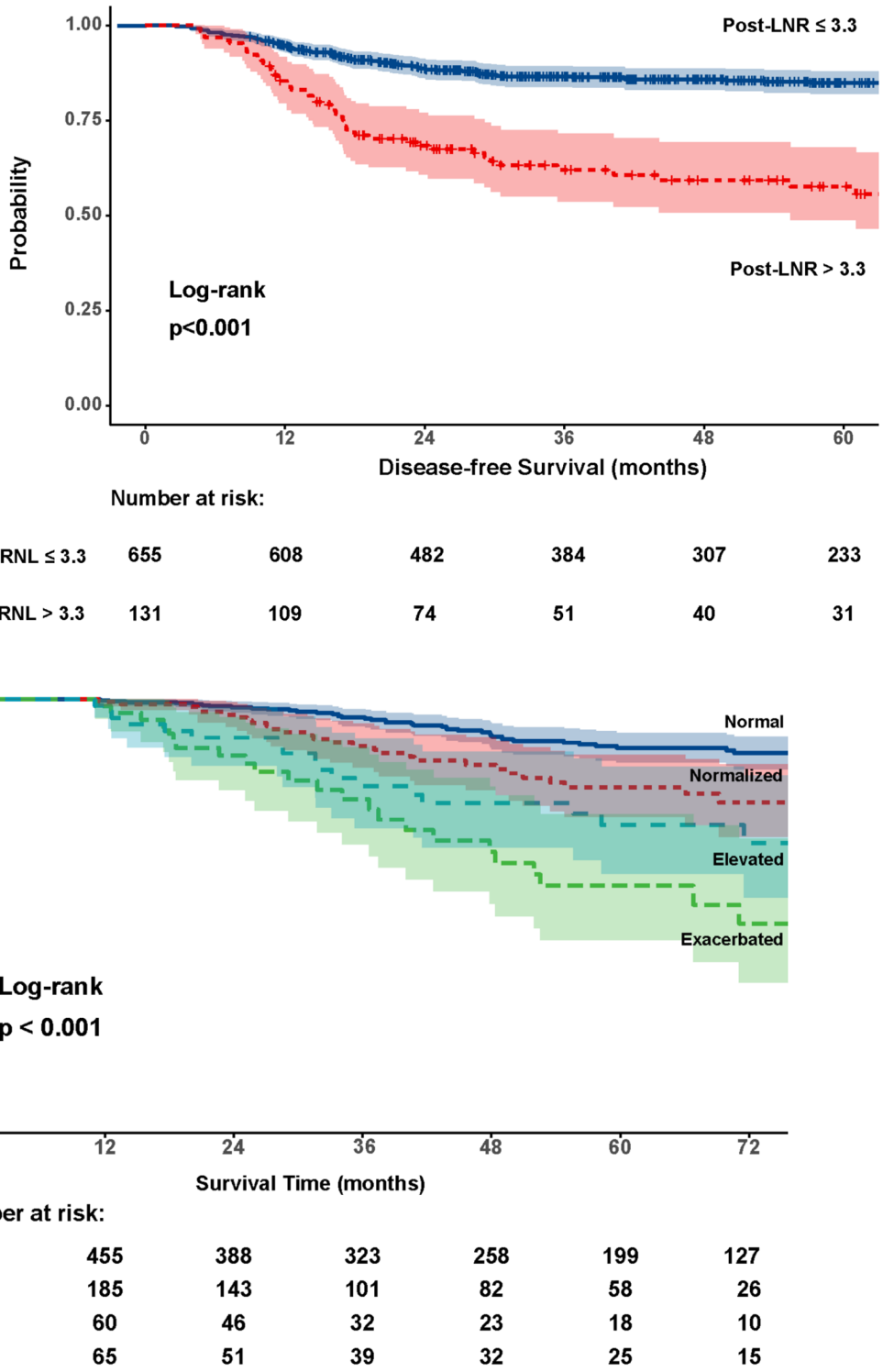

Fig. 4 Disease-free survival analysis for patients with post-NLR ≤ 3.3 versus post-NLR > 3 ($p < 0.001$). Log-rank test. Note: Two patients developed a recurrence just before one-year of follow-up

Fig. 5 Survival curves of the different subgroups according to NLR changes observed between before and after colorectal cancer surgery. Log-rank test

2.23, 95%CI 1.52–3.26), rectal location ($p < 0.001$; OR: 3.13, 95%CI 2.26–4.88), tumor stage ($p < 0.001$; OR: 1.36,

Table 2 Univariate analysis of persistent elevation of NLR 1 year after surgery. *Statistically significant. OR: Odds Ratio. 95% CI: 95% Confidence Interval

	Total N (%) 788 (100)	Post-NLR ≤ 3.3 N (%) 657 (83.4)	Post-NLR > 3.3 N (%) 131 (16.6)	p	OR (95% CI)
Age Median (IQR)	69.0 (62.0–76.0)	69.0 (62.0–76.0)	70.0 (57.0–77.0)	0.265	0.99 (0.97–1.01)
Sex:					
Men	483 (61.3)	394 (60.0)	89 (67.9)	0.088	0.71 (0.47–1.05)
Women	305 (38.7)	263 (40.0)	42 (32.1)		
Charlson score Median (IQR)	3.0 (2.0–3.0)	2.0 (2.0–3.0)	3.0 (2.0–4.0)	< 0.001*	1.25 (1.11–1.40)
BMI Median (IQR)	27.0 (24.0–29.4)	27.0 (24.0–29.4)	27.0 (24.0–29.0)	0.896	1.00 (0.96–1.05)
Basal NLR Median (IQR)	2.58 (1.83–3.67)	2.46 (1.73–3.45)	3.25 (2.24–4.83)	< 0.001*	1.27 (1.16–1.39)
Basal NLR categorized:					
≤ 3.3	537 (68.1)	468 (71.2)	69 (52.7)	< 0.001*	2.23 (1.52–3.26)
> 3	251 (31.9)	189 (28.8)	62 (47.3)		
Tumor location					
Colon	554 (70.3)	492 (74.9)	62 (47.3)	< 0.001*	3.13 (2.26–4.88)
Rectum	234 (29.7)	165 (25.1)	69 (52.7)		
Tumor stage					
I	174 (22.1)	152 (23.1)	22 (16.8)	0.005*	1.36 (1.10–1.70)
II	281 (35.7)	240 (36.5)	41 (31.3)		
III	277 (35.2)	225 (34.2)	52 (39.7)		
IV	56 (7.1)	40 (6.1)	16 (12.2)		
Nodal stage					
N0	553 (70.2)	467 (71.1)	86 (65.6)	0.215	1.29 (0.86–1.92)
N +	235 (29.8)	190 (28.9)	45 (34.4)		
Lymphovascular invasion					
No	548 (69.5)	456 (69.4)	92 (70.2)	0.852	0.96 (0.64–1.45)
Yes	240 (30.5)	201 (30.6)	39 (29.8)		
Perineural invasion					
No	617 (78.3)	515 (78.4)	102 (77.9)	0.894	1.03 (0.66–1.62)
Yes	171 (21.7)	142 (21.6)	29 (22.1)		
Postoperative complications:					
No	537 (68.1)	456 (69.4)	81 (61.8)	0.074	1.25 (0.98–1.61)
Minor	149 (18.9)	121 (18.4)	28 (21.4)		
Severe	102 (12.9)	80 (12.2)	22 (16.8)		
Neoadjuvant therapy					
No	654 (83.0)	571 (86.9)	83 (63.4)		
Yes	134 (17.0)	86 (13.1)	48 (36.6)		
Adjuvant therapy					
No	444 (56.3)	377 (57.4)	67 (51.1)	0.189	1.29 (0.88–1.87)
Yes	344 (43.7)	280 (42.6)	64 (48.9)		
Recurrence in follow-up:					
No	649 (82.4)	568 (86.5)	81 (61.8)	< 0.001*	3.94 (2.60–5.98)
Yes	139 (17.6)	89 (13.5)	50 (38.2)		
Dead in follow-up					
No	666 (84.5)	580 (88.3)	86 (65.6)	< 0.001*	3.94 (2.56–6.10)
Yes	122 (15.5)	77 (11.7)	45 (34.4)		

95%CI 1.10–1.70), and neoadjuvant therapy ($p < 0.001$; OR: 3.84, 95%CI 2.52–5.85).

Multivariate analysis

The following variables were entered in a Cox regression model: post-NLR (≤ 3.3 vs > 3), comorbidity measured by Charlson score, tumor stage, and rectal location. Collinearity was detected between variable rectal location and neoadjuvant therapy, so neoadjuvant therapy variable was not included. Post-RNL ($p < 0.001$; HR: 3.37, 95%CI 2.26–5.02), tumor stage ($p = 0.009$; HR: 1.32, 95%CI 1.07–1.62), comorbidity ($p < 0.001$; HR: 1.24, 95%CI 1.11–1.37), and rectal location ($p = 0.005$; HR: 0.54, 95%CI 0.35–0.83) remained independent predictors of long-term survival after 1 year of surgery (Fig. 6).

Discussion

The results of this study, using NLR as an inflammatory marker, confirm the importance of the patient's inflammatory status in colorectal cancer prognosis 1 year after surgery. Based on the results obtained, patients with post-NLR > 3.3 are four times more likely to experience recurrence or death. Multivariate analysis identified post-NLR as an independent prognostic factor, even after adjusting for tumor stage, comorbidity, and tumor location. Therefore, the presence of post-NLR levels > 3 1 year after surgery defines a population of patients operated on for CRC at very high risk of recurrence and death during follow-up. Other authors have reached the similar conclusions with different NLR cut-off points [20, 22–24], although in one study, NLR was not subject to significant overall change from the pre- to postoperative period [24].

Both preoperative and postoperative NLR are useful prognostic factors for survival and recurrence. However, most of the studies suggest that post-NLR is a stronger predictor [20]. This supports the idea that tumor removal may enhance immune function, making posttreatment NLR a reliable indicator of future recurrence [25].

Post-NLR levels have been assessed either as absolute values at a specific time after surgery [22, 25, 26], or by considering the dynamics of longitudinal changes in their values at different postoperative times [21, 23, 27].

We believe that one of the most interesting aspects in these cases is to evaluate changes in inflammatory status between pre- and postoperative periods, 1 year after surgery in our study. We found that the type of variation observed after curative CRC resection in the inflammation-based prognostic marker NLR values has a clear prognostic impact on tumor recurrence and long-term survival.

Our study demonstrates that, after resection of colorectal neoplasia, in most patients, the post-LNR values are maintained (normal subgroup: "low-low") or decrease significantly with respect to baseline NLR (normalized subgroup: "high-low"), indicating a good prognosis. However, those with persistently high NLR (elevated group: "high-high")

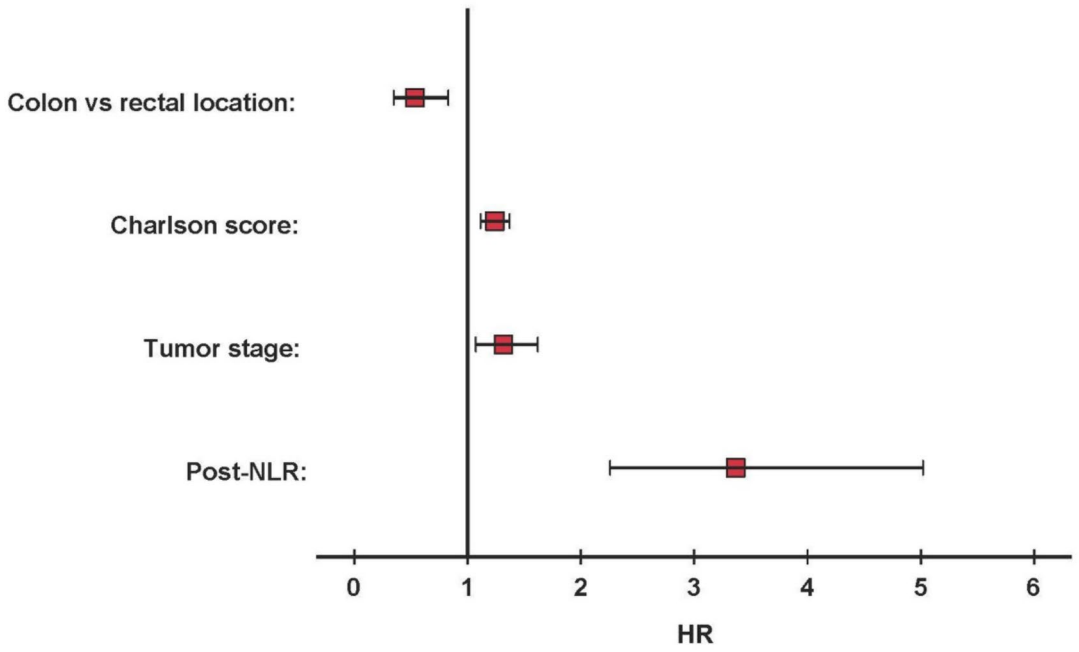

Fig. 6 Forest plot for survival of patients with colorectal cancer 1 year after curative resection based on multivariate Cox proportional hazard model

or an increase from low to high levels (elevated group: "low–high") after 1 year from surgery have a worse prognosis, as reflected in survival curves.

These findings are consistent with those reported by other authors [21] with different NLR cut-off points and different blood sampling times during follow-up. However, one study [20] reported that the exacerbation subgroup ("low–high") had a similar prognosis to the persistently normal subgroup ("low-low"). Shibutani et al. [22] also found that the "low-low" subgroup had a better prognosis in survival compared to the remaining subgroups, but they did no find significant differences among these other subgroups.

Therefore, changes in NLR may reflect treatment efficacy and its impact on survival [21, 23, 25]. However, three questions arise regarding the use of post-NLR as a prognostic factor in patients operated on by colorectal cancer.

First, whether NLR is the most appropriate inflammatory marker in these situations. Several inflammatory markers have been proposed for this purpose, including some prognostic scales [28], but many comparative studies have demonstrated its superiority to other markers [8, 29]. We believe that the NLR is the most accessible and cost-effective option.

Second, there were also very notable differences among the various published series regarding the timing of blood sampling to assess postoperative NLR levels: 21–56 days [21], 21–90 days [20], 1 month [22, 23, 25], between 1 and 3 months [26], between 3 and 6 months [24]. Our study used a 1-year timeframe, allowing sufficient time to minimize the influence of surgical trauma or adjuvant therapy on hematologic parameters.

Third, there is still no consensus on the optimal NLR cut-off value for CRC prognosis. Normal NLR values in healthy adults range from 0.78 to 3.53 [30], while in CRC patients, cut-offs typically range from 2 to 5 [7]. Most studies in patients with CRC have used a threshold around 3 [21, 22, 25, 26], which closely aligns with our chosen cut-off of 3.3.

The mechanism underlying and the significance of the persistent elevation of the systemic inflammatory response in patients who have undergone resection of the primary CRC (subgroup "high-high") remain unclear. It is thought that may reflect the complex interaction between the local immune response at the tumor microenvironment and the systemic inflammatory response [21].

There is sufficient evidence of the inflammatory pathogenesis of colorectal cancer [4]. Proinflammatory systemic factors can act as initiators of carcinogenesis, and, during neoplastic transformation, tumor cells also release proinflammatory substances which contribute to creating a situation of systemic inflammation [5]. At the same time, certain substances released by tumor associated neutrophils may act to promote tumor growth [31]. On the other hand, lymphocytes, both peripheral blood and tumor infiltrating lymphocytes, play a key role in antitumor immunity [32]. In fact, the absolute lymphocyte count is assumed to reflect the degree of responsiveness of a cancer patient's whole immune system [33]. This would explain why patients with elevated NLR levels would have a worse prognosis. Therefore, a persistently high NLR after surgery means the continuation of an environment that is favorable for recurrence.

From a clinical point of view, some authors [21, 22, 24, 25] have already suggested the more than possible association between postoperative high levels of neutrophil–lymphocyte ratio and the presence of minimal residual disease or early metastatic disease in these patients. Murray et al. [25] defined minimal residual disease as bone marrow micro-metastases and circulating tumor cells, noting that NLR only decreased in patients without these circulating cells. Their presence was associated with immune dysfunction and poorer prognosis.

However, Yasui et al. [20] suggest that persistently high inflammatory markers may reflect a patient's intrinsic inflammatory state. To demonstrate this, they analyzed various prognostic markers, including NLR, in the "elevated" subgroup 5 years post-surgery without recurrence. Over 90% maintained high inflammation levels, though initial tumor stage data were not provided.

Our results support the hypothesis that high NLR levels 1 year after surgery often indicate undetectable disease progression. Survival curves confirm this trend. In addition, the univariate analysis revealed that patients with high post-NLR levels typically had more advanced disease. However, it is questionable whether the response to the micrometastatic lesion and the response to the primary tumor are equivalent [22].

Univariate analysis identified comorbidity, neoadjuvant therapy, and tumor location as potential confounders, alongside tumor stage. Regarding tumor stage, all included stage IV cases met stringent criteria for curative resection. These patients represent a distinct subgroup with potentially favorable long-term outcomes [34], and for this reason, they were not excluded from the study. In addition, acknowledging the potential for confounding, we included tumor stage, post-NLR, tumor location, and comorbidity as covariates in the multivariate analysis, with the intention to adjust for their possible influence on survival outcomes. Tumor stage emerged as an independent prognostic factor. These findings support the relevance of post-NLR assessment even in patients with stage IV disease.

Comorbidity was strongly associated with post-NLR and is known to predict higher mortality in cancer patients, including CRC, particularly from cardiovascular causes [35]. Comorbidity could also have influenced survival because of its relationship with the poor tolerance to chemotherapy that some of these patients would present [36]. These data were not analyzed in our study.

With respect to tumor location, it has been suggested that there is a greater inflammatory response in rectal cancer than in colon cancer, which may explain why preoperative NLR is not always an independent survival predictor in patients with rectal cancer [37]. Additionally, neoadjuvant radiotherapy, common in rectal cancer, may induce a prolonged inflammatory response, contributing to elevated post-NLR levels.

Limitations of this study include the single-center and retrospective study design. Its retrospective design may introduce selection bias and unmeasured confounding factors. Additionally, genetic status data (KRAS, BRAF, and microsatellite instability), which may play an important role in the prognosis of the neoplasm, were not analyzed. Strengths include a large, representative sample, standardized blood collection timing, and the use of a single reference point (1 year post-surgery) to assess NLR's prognostic significance. Data were also collected prospectively, and control for potential confounders was performed by multivariate analysis.

Conclusions

Our study underscores the prognostic value of NLR 1 year after colorectal cancer surgery. Elevated pre- and post-NLR levels correlate with poorer survival, suggesting a role for persistent inflammation in disease progression. Patients with increasing or consistently high NLR have worse outcomes. Future research should assess NLR's role in treatment decisions and its integration into prognostic models. NLR should be routinely included in blood test reports.

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Data availability The data sets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval The study was approved by the institution's Clinical Ethics and Research Committee (*CEI/CEIm Hospital Universitario de Gran Canaria Doctor Negrín 2020-279-1*).

Informed consent The need for informed consent was waived due to the retrospective nature of the study.

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References

1. Siegel RL, Wagle NS, Cercek A et al (2023) Colorectal cancer statistics, 2023. CA Cancer J Clin 73:233–254. https://doi.org/10.3322/caac.21772
2. Perez-Palma J, Marchena-Gomez J, Dorta-Espineira M et al (2008) Predictive factors of years of potential life lost by colorectal cancer. Eur J Gastroenterol Hepatol 20:766–772. https://doi.org/10.1097/MEG.0B013E3282FBF5D3
3. Puerta-García E, Cañadas-Garre M, Calleja-Hernández MÁ (2015) Molecular biomarkers in colorectal carcinoma. Pharmacogenomics 16:1189–1222. https://doi.org/10.2217/PGS.15.63
4. Schmitt M, Greten FR (2021) The inflammatory pathogenesis of colorectal cancer. Nat Rev Immunol 21:653–667. https://doi.org/10.1038/s41577-021-00534-x
5. Tuomisto AE, Mäkinen MJ, Väyrynen JP (2019) Systemic inflammation in colorectal cancer: underlying factors, effects, and prognostic significance. World J Gastroenterol 25:4383–4404. https://doi.org/10.3748/wjg.v25.i31.4383
6. Park JH, Watt DG, Roxburgh CSD et al (2016) Colorectal cancer, systemic inflammation, and outcome. Ann Surg 263:326–336. https://doi.org/10.1097/SLA.0000000000001122
7. Misiewicz A, Dymicka-Piekarska V (2023) Fashionable, but What is their real clinical usefulness? NLR, LMR, and PLR as a promising indicator in colorectal cancer prognosis: a systematic review. J Inflamm Res 16:69–81. https://doi.org/10.2147/JIR.S391932
8. Song Y, Yang Y, Gao P et al (2017) The preoperative neutrophil to lymphocyte ratio is a superior indicator of prognosis compared with other inflammatory biomarkers in resectable colorectal cancer. BMC Cancer 17:744. https://doi.org/10.1186/s12885-017-3752-0
9. Ortiz López D, Marchena Gómez J, NoguésRamia EM et al (2024) Prognostic value of neutrophil-to-lymphocyte ratio at diagnosis in colorectal cancer: propensity score analysis. Rev Esp Enferm Dig 116:408–415. https://doi.org/10.17235/reed.2024.10041/2023
10. Mazaki J, Katsumata K, Kasahara K et al (2020) Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: a propensity score analysis. BMC Cancer. https://doi.org/10.1186/s12885-020-07429-5

11. Malietzis G, Giacometti M, Kennedy RH et al (2014) The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. Ann Surg Oncol 21:3938–3946. https://doi.org/10.1245/S10434-014-3815-2
12. Naszai M, Kurjan A, Maughan TS (2021) The prognostic utility of pre-treatment neutrophil-to-lymphocyte ratio (NLR) in colorectal cancer: a systematic review and meta-analysis. Cancer Med 10:5983–5997. https://doi.org/10.1002/cam4.4143
13. Li H, Zhao Y, Zheng F (2019) Prognostic significance of elevated preoperative neutrophil-to-lymphocyte ratio for patients with colorectal cancer undergoing curative surgery. Medicine 98:e14126. https://doi.org/10.1097/MD.0000000000014126
14. Haram A, Boland MR, Kelly ME et al (2017) The prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review. J Surg Oncol 115:470–479. https://doi.org/10.1002/JSO.24523
15. Tsai PL, Su WJ, Leung WH et al (2016) Neutrophil-lymphocyte ratio and CEA level as prognostic and predictive factors in colorectal cancer: a systematic review and meta-analysis. J Cancer Res Ther 12:582–589. https://doi.org/10.4103/0973-1482.144356
16. Amin MB, Gress DM, Meyer-Vega LR et al (2017) AJCC cancer staging manual, 8th edn. Springer, Berlin
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383. https://doi.org/10.1016/0021-9681(87)90171-8
18. Youden WJ (1950) Index for rating diagnostic tests. Cancer 3:32–35. https://doi.org/10.1002/1097-0142(1950)3:1%3c32::AID-CNCR2820030106%3e3.0.CO;2-3
19. Clavien PA, Barkun J, de Oliveira ML et al (2009) The clavien-dindo classification of surgical complications. Ann Surg 250:187–196. https://doi.org/10.1097/SLA.0b013e3181b13ca2
20. Yasui K, Shida D, Nakamura Y et al (2021) Postoperative, but not preoperative, inflammation-based prognostic markers are prognostic factors in stage III colorectal cancer patients. Br J Cancer 124:933–941. https://doi.org/10.1038/s41416-020-01189-6
21. Chan JCY, Diakos CI, Chan DLH et al (2018) A longitudinal investigation of inflammatory markers in colorectal cancer patients perioperatively demonstrates benefit in serial remeasurement. Ann Surg 267:1119–1125. https://doi.org/10.1097/SLA.0000000000002251
22. Shibutani M, Maeda K, Nagahara H et al (2015) The prognostic significance of a postoperative systemic inflammatory response in patients with colorectal cancer. World J Surg Oncol 13:1–8. https://doi.org/10.1186/S12957-015-0609-3
23. Guo D, Han A, Jing W et al (2018) Preoperative to postoperative change in neutrophil-to-lymphocyte ratio predict survival in colorectal cancer patients. Future Oncol 14:1187–1196. https://doi.org/10.2217/FON-2017-0659
24. Guthrie GJK, Roxburgh CSD, Farhan-Alanie OM et al (2013) Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. Br J Cancer 109:24–28. https://doi.org/10.1038/BJC.2013.330
25. Murray NP, Villalon R, Orrego S, Guzman E (2021) The association of the neutrophil-lymphocyte ratio with the presence of minimal residual disease and outcome in patients with Stage II colon cancer treated with surgery alone. Colorectal Dis 23:805–813. https://doi.org/10.1111/CODI.15438
26. Li Z, Zhao R, Cui Y et al (2018) The dynamic change of neutrophil to lymphocyte ratio can predict clinical outcome in stage I-III colon cancer. Sci Rep. https://doi.org/10.1038/s41598-018-27896-y
27. Ashizawa N, Furuya S, Katsutoshi S et al (2020) Clinical significance of dynamic neutrophil-lymphocyte ratio changes in patients with colorectal cancer. Anticancer Res 40:2311–2317. https://doi.org/10.21873/ANTICANRES.14197
28. McMillan DC (2013) The systemic inflammation-based Glasgow prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev 39:534–540. https://doi.org/10.1016/j.ctrv.2012.08.003
29. Choi WJ, Cleghorn MC, Jiang H et al (2015) Preoperative neutrophil-to-lymphocyte ratio is a better prognostic serum biomarker than platelet-to-lymphocyte ratio in patients undergoing resection for nonmetastatic colorectal cancer. Ann Surg Oncol 22:603–613. https://doi.org/10.1245/s10434-015-4571-7
30. Forget P, Khalifa C, Defour J-P et al (2017) What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes 10:12. https://doi.org/10.1186/s13104-016-2335-5
31. Mizuno R, Kawada K, Itatani Y et al (2019) The role of tumor-associated neutrophils in colorectal cancer. Int J Mol Sci 20:529. https://doi.org/10.3390/IJMS20030529
32. Zhao J, Huang W, Wu Y et al (2020) Prognostic role of pretreatment blood lymphocyte count in patients with solid tumors: a systematic review and meta-analysis. Cancer Cell Int 20:1–14. https://doi.org/10.1186/S12935-020-1094-5/TABLES/3
33. Shibutani M, Maeda K, Nagahara H et al (2021) Lymphopenia associated with adjuvant chemotherapy after potentially curative surgery for colorectal cancer correlates with recurrence. Int Surg 105:146–151. https://doi.org/10.9738/INTSURG-D-14-00236.1
34. Yi C, Li J, Tang F et al (2020) Is primary tumor excision and specific metastases sites resection associated with improved survival in stage IV colorectal cancer? Results from SEER database analysis. Am Surg 86:499–507. https://doi.org/10.1177/0003134820919729
35. He Y, Liu X, Wang M et al (2024) Neutrophil-to-lymphocyte ratio as a predictor of cardiovascular mortality in cancer survivors. Sci Rep 14:20980. https://doi.org/10.1038/S41598-024-72027-5
36. Sarfati D, Koczwara B, Jackson C (2016) The impact of comorbidity on cancer and its treatment. CA Cancer J Clin 66:337–350. https://doi.org/10.3322/CAAC.21342
37. Chiang S-F, Hung H-Y, Tang R et al (2012) Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis 27:1347–1357. https://doi.org/10.1007/s00384-012-1459-x

6. CONCLUSIONES

En vista de los resultados obtenidos tras el desarrollo de esta investigación, podemos concluir que:

1) Las complicaciones postoperatorias tras cirugía por cáncer colorrectal, evaluadas mediante el índice CCI (*Comprehensive Complication Index*), se asocian con resultados oncológicos adversos. Se necesitan esfuerzos para reducir tanto la incidencia como la severidad de estas complicaciones, dado su impacto en la supervivencia a largo plazo.
   La escala S-CRC-PC (*Surgical - Colorectal Cancer - Postoperative Complications*), que incorpora por primera vez las complicaciones postoperatorias junto con variables clásicas como el estadio tumoral (TNM), la edad del paciente y las comorbilidades, podría resultar una herramienta útil para predecir los resultados oncológicos a largo plazo.

2) Los niveles de Proteína C Reactiva (PCR) en el cuarto día postoperatorio muestran una relación estadísticamente significativa con la aparición de cualquier tipo de complicación postoperatoria, no solo con la dehiscencia anastomótica. Además, se observa una correlación positiva entre la puntuación del CCI y los valores de PCR.
   Según nuestros resultados, un nivel de PCR < 42 mg/L en el cuarto día postoperatorio permite descartar con seguridad la aparición de complicaciones postoperatorias, lo que podría ser útil como marcador precoz de evolución favorable.

3) El índice neutrófilo-linfocito (INL) basal elevado (> 3.3) en pacientes con cáncer colorrectal en el momento del diagnóstico representa un factor de mal pronóstico en términos de supervivencia. Se trata de un parámetro sencillo, reproducible y de bajo coste, obtenido a partir de un hemograma convencional.
   La incorporación del INL en la práctica clínica rutinaria podría ayudar a identificar a los pacientes con mayor riesgo de progresión tumoral, permitiendo intensificar las estrategias terapéuticas (como la selección de regímenes de quimioterapia más agresivos o terapias adyuvantes) y optimizar el seguimiento en este subgrupo de alto riesgo. Futuros estudios deberán validar su utilidad en algoritmos pronósticos integrados con otros marcadores clínicos y moleculares.

4) El INL al año de la cirugía por CCR se relaciona con el pronóstico oncológico. La elevación del valor al diagnóstico y al año de la cirugía se asocia con una menor supervivencia, lo que sugiere un papel relevante de la inflamación persistente en la progresión de la enfermedad. Los pacientes con una elevación mantenida o progresiva a lo largo del proceso oncológico presentan peores resultados clínicos.

9. RESUMEN

INTRODUCCIÓN

El cáncer colorrectal representa una de las principales causas de incidencia y mortalidad por cáncer a nivel mundial. Aunque se han establecido múltiples factores pronósticos, estos podrían presentar limitaciones al no considerar aspectos como la respuesta inflamatoria sistémica del paciente o la aparición de complicaciones postoperatorias, elementos que pueden influir en el pronóstico. En este contexto, diversos estudios han señalado el valor potencial de biomarcadores inflamatorios accesibles y económicos, como la proteína C reactiva y el índice neutrófilo-linfocito, así como herramientas más sensibles para cuantificar la carga de morbilidad postoperatoria, como el *Comprehensive Complication Index*.

OBJETIVOS

Esta investigación se propuso analizar de manera conjunta el valor clínico de las complicaciones postoperatorias, el comportamiento de la proteína C reactiva en el postoperatorio inmediato y el valor pronóstico del índice neutrófilo-linfocito tanto en el momento del diagnóstico como un año después de la cirugía y su relación con el pronóstico del cáncer colorrectal.

RESULTADOS

Los resultados obtenidos muestran que las complicaciones postoperatorias, evaluadas mediante el *Comprehensive Complication Index*, se asocian de forma independiente con un peor pronóstico oncológico a largo plazo. A partir de esta observación se desarrolló una nueva escala pronóstica, denominada S-CRC-PC, que integra el índice de complicaciones con factores clásicos como el estadio tumoral, la edad del paciente y la presencia de comorbilidades. Por otro lado, se observó que la proteína C reactiva en el cuarto día postoperatorio se correlaciona significativamente con la aparición de cualquier tipo de complicación, no solo con la dehiscencia anastomótica, destacando un valor umbral de 42 mg/L por debajo del cual puede asumirse una evolución favorable. En cuanto al índice neutrófilo-linfocito, se evidenció que valores elevados en el momento del diagnóstico se asocian con una menor supervivencia global y específica, confirmando su utilidad como marcador pronóstico temprano. Asimismo, el análisis del índice un año después de la cirugía demostró que una elevación persistente se relaciona con peores resultados clínicos, reforzando la hipótesis del papel relevante de la inflamación sistémica mantenida en la progresión tumoral.

CONCLUSIONES

En conjunto, los hallazgos de este trabajo confirman la relevancia de adoptar un enfoque integral en el abordaje del cáncer colorrectal, que no se limite exclusivamente a las características del tumor, sino que contemple también la respuesta biológica del paciente y los eventos clínicos ocurridos durante el proceso terapéutico. La incorporación de marcadores inflamatorios sistémicos accesibles, como la proteína C reactiva y el índice neutrófilo-linfocito, junto con una valoración cuantitativa de las complicaciones postoperatorias a través del *Comprehensive Complication Index*, podría aportar una estratificación pronóstica precisa, personalizada y coste-efectiva.

PALABRAS CLAVE

Cáncer colorrectal; factores pronósticos; complicaciones postoperatorias; *Comprehensive Complication Index*; proteína C Reactiva; índice neutrófilo-linfocito

10. SUMMARY

INTRODUCTION

Colorectal cancer is one of the leading causes of cancer incidence and mortality worldwide. Although numerous prognostic factors have been established, they may present limitations by failing to account for variables such as the patient's systemic inflammatory response or the occurrence of postoperative complications—elements that can significantly influence clinical outcomes. In this context, various studies have highlighted the potential prognostic value of accessible and cost-effective inflammatory biomarkers, such as C-reactive protein and the neutrophil-to-lymphocyte ratio, as well as more sensitive tools for quantifying postoperative morbidity burden, such as the Comprehensive Complication Index.

OBJECTIVES

This research aimed to jointly assess the clinical impact of postoperative complications, the behaviour of C-reactive protein in the immediate postoperative period, and the prognostic significance of the neutrophil-to-lymphocyte ratio, both at the time of diagnosis and one year following surgery, in relation to colorectal cancer prognosis.

RESULTS

The findings indicate that postoperative complications, when assessed using the Comprehensive Complication Index, are independently associated with worse long-term oncological outcomes. Based on this observation, a new prognostic scale—termed S-CRC-PC—was developed, integrating the CCI with traditional variables such as tumour stage, patient age, and comorbidities. Furthermore, CRP levels on postoperative day four were found to correlate significantly with the occurrence of any type of complication—not solely anastomotic leakage—highlighting a threshold of 42 mg/L below which favourable clinical progression may be assumed. Regarding the neutrophil-to-lymphocyte ratio, elevated values at diagnosis were associated with reduced overall and cancer-specific survival, supporting its utility as an early prognostic marker. Additionally, NLR measured one year after surgery showed that persistent elevation was linked to poorer clinical outcomes, reinforcing the hypothesis that sustained systemic inflammation plays a crucial role in tumour progression.

CONCLUSIONS

Taken together, these findings underscore the importance of adopting a comprehensive approach in the management of colorectal cancer—one that goes beyond tumour-

specific characteristics to also encompass the patient's biological response and perioperative clinical events. The incorporation of accessible systemic inflammatory markers, such as CRP and NLR, alongside a quantitative assessment of postoperative complications through the Comprehensive Complication Index, may offer a more accurate, individualised, and cost-effective method for prognostic stratification.

KEYWORDS

Colorectal cancer; prognostic factors; postoperative complications; Comprehensive Complication Index; C reactive protein; neutrophil-to-lymphocyte ratio