Safety of different electrocautery modes for endoscopic sphincterotomy: a Bayesian network meta-analysis

Abdellah Hedjoudje, Chérifa Cheurfa, Jad Farha, Bénédicte Jaïs, Alain Aubert, Diane Lorenzo, Frédérique Maire, Dilhana Badurdeen, Vivek Kumbhari and Frédéric Prat

Abstract

Background and aims: Post-endoscopic retrograde cholangiopancreatography acute pancreatitis (PAP) and post-sphincterotomy hemorrhage are known adverse events of post-endoscopic retrograde cholangiopancreatography. Various electrosurgical currents can be used for endoscopic sphincterotomy. The extent to which this influences adverse events remains unclear. We assessed the comparative safety of different electrosurgical currents, through a Bayesian network meta-analysis of published studies merging direct and indirect comparison of trials.

Methods: We performed a Bayesian random-effects network meta-analysis of randomized controlled trials that compared the safety of different electrocautery modes for endoscopic sphincterotomy.

Results: Nine studies comparing four electrocautery modes (blended cut, pure cut, endocut, and pure cut followed by blended cut) with a combined enrollment of 1615 patients were included. The pooled results of the network meta-analysis did not show a significant difference in preventing post-sphincterotomy pancreatitis when comparing electrocautery modes. However, pure cut was associated with a statistically significant increased risk of bleeding compared with endocut [relative risk = 4.30; 95% confidence interval (1.53–12.87)]. On the other hand, the pooled results of the network meta-analysis showed no significant difference in prevention of bleeding when comparing blended cut versus endocut, pure cut followed by blended cut versus endocut, pure cut versus blended cut, and pure cut versus pure cut followed by blended cut. The results of rank probability found that endocut was most likely to be ranked the best.

Conclusion: No electrocautery mode was superior to another with regard to preventing PAP. Endocut was superior with respect to preventing bleeding. Therefore, we suggest performing endoscopic sphincterotomy with endocut.

Keywords: electrocautery, electrocoagulation, endoscopic sphincterotomy, endoscopic retrograde cholangiopancreatography, pancreatitis

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of pancreatitis and bleeding were 5.4% and 2%, respectively. Acute pancreatitis remains the most frequent adverse event associated with the procedures, despite innumerable efforts at preventing its development with drugs and/or pancreatic stents, but papillary bleeding also remains serious, particularly in patients under anticoagulant and/or antiplatelet agents.

The characteristics of the electrosurgical current can affect the risk of complications of endoscopic sphincterotomy (ES) because of the different nature of thermal tissue injury produced. A high-voltage, pure cutting current develops high tissue cutting ability and therefore achieves rapid and precise sphincter section, whereas a low-voltage coagulating current provides better hemostasis. A blend of both pure cutting and coagulating currents is available on high frequency (HF) generators designed for endoscopic procedures under the blended current label, while generator manufacturers, initially Erbe Medizin in the 1990s, later followed by others, developed new settings for sphincterotomy, polypectomy, and other techniques under the ‘Endocut’ label, which deliver sequential short bursts of pure or blended current followed by coagulation in a feedback loop between the electrical impedance of the tissue and the amount of energy delivered. Compared with the conventional blended mode, the endocut (EC) can provide with a precise and continuous degree of coagulation of the incision margins for hemostasis by its automatic voltage regulation and controlled cutting speed. This automatically fractionated cut aims to avoid perforation of the upper part of the papilla which can result from an uncontrolled cutting speed and may thus theoretically reduce complications of sphincterotomy.

There are, however, contradictory reports as to the respective risks of the development of acute pancreatitis and bleeding in multiple clinical trials comparing the pure cut (PC), EC, and the blended modes. Underpowerment and retrospective analysis have seriously limited the value of previous studies, making it difficult to gain definitive conclusions on the efficacy and safety of the different HF currents. To overcome those limitations, we made use of the direct and indirect evidence through a Bayesian network meta-analysis (NMA).

**Methods**

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analysis (PRISMA-NMA) guidelines.

**Search strategy**

A literature search was conducted in four databases including MEDLINE through PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and Web of Science from inception to April 2020 to identify potentially relevant studies. We did not limit searching by publication date or language. MEDLINE search strategy is detailed in Supplemental File 1. Search equation for the different databases was developed from PubMed search equation. We also evaluated the reference lists of the relevant clinical trials to identify additional studies.

**Study selection**

In a first step, titles and abstracts of articles were screened independently by two reviewers to exclude irrelevant articles. Then, the full text of all selected studies was screened according to predefined inclusion and exclusion criteria. Included studies were exclusively randomized controlled with the following criteria: (1) adult patients undergoing sphincterotomy, (2) intervention: sphincterotomy with different electrical modes, (3) comparator: another electrical current mode, and (4) outcome: pancreatitis or bleeding. We excluded (1) nonrandomized controlled studies, (2) trials not comparing different electrical modes such as prophylactic stent or nonsteroidal anti-inflammatory drugs (NSAIDs), (3) case reports, meta-analyses, and nonrandomized trials, (4) language other than English, or (5) not involving human beings. Two reviewers (AH and CC) independently evaluated the studies for eligibility. Any disagreements were solved through discussion with the third investigator (FP).

**Data extraction and quality assessment**

Two reviewers (AH and CC) independently extracted data using a predefined extraction form. Extracted data were the following: the first author name, publication year, study period and design, and country. Patient’s baseline characteristics were age and sex, indication for ERCP, and adverse events including pancreatitis, bleeding, cholangitis, or perforation. The qualities of randomized clinical trials were assessed using the risk of bias tool recommended by the Cochrane
Collaboration on several dimensions: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; and (5) incomplete outcome data, as recommended by the Cochrane handbook. Any disagreement in data extraction was resolved through consensus and discussion with a third reviewer (FP).

Statistical analysis
In the first step, multiple direct pairwise meta-analysis was performed using a fixed random-effects model to estimate pooled relative risk (RR) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using $I^2$ statistic, with values less than 25% indicating no heterogeneity, between 25% and 50% indicating moderate heterogeneity, and more than 50% indicating substantial heterogeneity and the Cochran’s $Q$ test. In the second step, a random-effects Bayesian NMA using the Markov chain Monte Carlo (MCMC) methods was conducted. NMA allows the comparison of evidence from clinical studies where directly comparative data are not available. The posterior distribution of all parameters was estimated using informative priors to limit inference to data derived from the trials at hand. NMA also enables the ranking of treatments in order of efficacy. Electrocautery method mode was ranked in each iteration according to their preventive effect for pancreatitis or bleeding, respectively. We assessed the probability that each intervention was the most efficacious in decreasing the rate of pancreatitis or bleeding, the second best, the third best, and so on, by calculating the surface area under the curve (SUCRA) for each current mode compared with an arbitrary common control group. A node-splitting method was used to check network consistency by comparing direct and indirect estimates. Pairwise and network meta-analyses were conducted using R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria) with the meta, GeMTC, and BUGSnet packages. Finally publication bias was explored quantitatively with Egger’s test and graphically with funnel plot.

Results

Study selection
From a total of 50 unique studies identified using the search strategy, we included nine randomized controlled trials (RCTs) in this NMA. Seven studies were published article and two were published as abstracts. The detailed steps of the study selection process are shown in Figure 1. The reasons for the exclusion of studies during the final review were as follows: not randomized ($n = 3$) or review or meta-analysis ($n = 4$). Figure 2 displays the available direct comparisons and network of trials and shows the network plot of relevant studies. Pure cut (PC) mode was the most widely used with 533 patients followed by blended cut (BC) mode with 522 patients, Endocut (EC) with 403 patients, and pure cut followed by blended (PC/BC) with 157.

Characteristics and quality of included studies
Table 1 summarizes the main characteristics of the included trials. Overall, the nine trials had 1615 participants. Seven of them were two-armed studies and two were three-armed. The age of patients ranged from 55 to 73 years. The main indication for ERCP was cholelithiasis in 69.7% (1025/1471) of patients, sphincter of Oddi dysfunction (SOD) in 7.3% (108/1471), and other indications in the remaining 30% (338/1471). These trials were published between 1998 and 2015 with an enrollment period from June 1994 to May 2011. All studies were at high risk of bias for at least one domain of the Cochrane risk of bias tool (Supplemental File 2). Devices used and outcome definitions used by authors are summarized in Supplemental File 3.

Acute pancreatitis
Supplemental File 4 shows direct comparisons using a traditional pair-wise meta-analysis. There was no statistical difference between the different electrocautery modes in rates of post-sphincterotomy pancreatitis. The pooled results of the NMA showed no significant difference when comparing EC versus BC [RR = 1.24; 95% CI (0.41–4.21)], PC versus BC [RR = 0.48; 95% CI (0.18–1.09)], PC/BC versus BC [RR = 0.84; 95% CI (0.25–2.82)], PC versus EC [RR = 0.28; 95% CI (0.06–1.32)], PC/BC versus EC [RR = 0.68; 95% CI (0.13–3.18)], or PC/BC versus PC [RR = 1.76; 95% CI (0.64–5.73)].

Combined direct and indirect estimates from the Bayesian NMA are demonstrated in Figure 3 and Table 2. The results of rank probability showed that PC was most likely to be ranked the best (rank probability: 63%) (Supplemental File 5A).
Bleeding
Supplemental File 6 shows direct comparisons using a traditional pair-wise meta-analysis. PC was associated with an increased risk of bleeding compared with EC \([RR = 4.34; 95\% CI (2.09–9.01)]\). There was no statistically significant difference between the other electrocautery modes.

Combined direct and indirect estimates from the Bayesian NMA are demonstrated in Figure 3 and Table 2. PC was associated with an increased risk of bleeding compared with EC \([RR = 4.29; 95\% CI (1.53–12.87)]\). However, the pooled results of the NMA showed no significant difference when comparing EC versus BC \([RR = 0.44; 95\% CI (0.34–3.95)]\), PC versus BC \([RR = 1.92; 95\% CI (0.71–2.91)]\), PC/BC versus BC \([RR = 1.02; 95\% CI (0.39–3.6)]\), PC/BC versus EC \([RR = 2.72; 95\% CI (0.72–12.95)]\), or PC/BC versus PC \([RR = 0.63; 95\% CI (0.23–2.07)]\). The results of rank probability found EC was most likely to be ranked the best concerning risk of bleeding (rank probability: 98%), followed by BC, PC/BC, and PC (Supplemental File 5B).

Publication bias and network coherence. No evidence for publication bias was found, neither quantitatively based on visual inspection of funnel plots and quantitatively based on Egger’s test, although the number of study for each comparison is small making these method less reliable. There were no significant differences between direct and indirect estimates when both were available, and the two methods had overlapping CIs for all interventions (Table 2 and Supplemental File 3).

Discussion
We hereby conducted the first NMA comparing the risks of adverse events associated with different
Figure 2. Network plot of relevant studies. Circles represent each electrocautery mode as a node and lines represent the direct comparisons. The extent of circle indicates the number of included participants in each electrocautery mode and the number on each blue line indicates the number of studies included in each comparison.

BC, blended cut; EC, endocut; PC, pure cut; PC/BC, pure cut followed by blended cut.

Figure 3. Forest plot of network estimate for the risk of post-ERCP acute pancreatitis with overall studies [a] and after excluding abstract [b]. [c] Forest plot of network estimate for the risk of bleeding [c] and after excluding abstract [d]. The summary effect estimate (risk ratio) is indicated by blue rectangles and lines representing 95% credible intervals.

BC, blended cut; EC, endocut; ERCP, endoscopic retrograde cholangiopancreatography; PC, pure cut; PC/BC, pure cut followed by blended cut.
Table 1. Baseline characteristics of randomized controlled trials comparing different electric current modes.

| First author, reference | Inclusion period | Location | Setting | Current mode | Number of patients | Age, mean (range) | Male | Indication for ES |
|--------------------------|------------------|----------|---------|--------------|-------------------|------------------|------|------------------|
|                          |                  |          |         |              |                   |                  |      |                  |
|                          |                  |          |         |              |                   |                  |      | Cholethiasis, N (%) | SOD, N (%) | Other, N (%) |
| Tanaka et al.\textsuperscript{20} | June 2006 to May 2011 | Japan | Multicenter | EC | 179 | 73 (23–97) median | 92 | 150 (83.8) | 0 (0) | 29 (16.2) |
|                          |                  |          |         | BC | 181 | 73 (30–101) median | 108 | 143 (79) | 0 (0) | 38 (21) |
| Norton et al.\textsuperscript{19} | NR | The United States | Multicenter | EC | 133 | 59 (19–92) | 70 | 63 (47.3) | 7 (5.26) | 73 (47.4) |
|                          |                  |          |         | PC | 134 | 59 (20–99) | 67 | 62 (46.2) | 5 (3.7) | 67 (50.1) |
| MacIntosh et al.\textsuperscript{21} | 1999–2002 | The United States | Single center | PC | 116 | NR | NR | 91 (78.4) | 9 (7.7) | 16 (13.8) |
|                          |                  |          |         | BC | 130 | NR | NR | 96 (73.8) | 10 (7.7) | 24 (18.5) |
| Stefanidis et al.\textsuperscript{22} | October 1999 to October 2001 | Greece | Single center | PC | 62 | 62 (40–82) | 35 | 62 (100) | 0 (0) | 0 (0) |
|                          |                  |          |         | BC | 62 | 66 (44–86) | 36 | 62 (100) | 0 (0) | 0 (0) |
|                          |                  |          |         | PC/BC | 62 | 64 (42–84) | 34 | 62 (100) | 0 (0) | 0 (0) |
| Gorelick et al.\textsuperscript{23} | June 1997 to November 1998 | The United States | Single center | PC | 75 | NR | 20 | 40 (53.3) | 23 (30.6) | 12 (16.1) |
|                          |                  |          |         | PC/BC | 67 | NR | 27 | 39 (58.2) | 18 (26.8) | 10 (15) |
| Kohler et al.\textsuperscript{7} | June–November 1994 | Germany | Single center | EC | 50 | NR | NR | 22 (44) | 0 (0) | 28 (56) |
|                          |                  |          |         | BC | 50 | NR | NR | 22 (44) | 0 (0) | 28 (56) |
| Elta et al.\textsuperscript{24} | November 1994 and June 1995 | The United States | Single center | PC | 86 | 51 (19–96) | 30 | 55 (63.9) | 18 (20.9) | 13 (15.2) |
|                          |                  |          |         | BC | 84 | 55 (21–92) | 30 | 56 (66.6) | 18 (21.4) | 13 (15.5) |
| Kida et al.\textsuperscript{25} | conference proceeding | From June 2002 to 2004 | Japan | Single center | EC | 41 | NR | NR | NR | NR | NR |
|                          |                  |          |         | PC | 43 | NR | NR | NR | NR | NR |
| Mahadeva et al.\textsuperscript{26} | conference proceeding | November 1998 to August 1999 | The United Kingdom | PC | 17 | NR | NR | NR | NR | NR | NR |
|                          |                  |          |         | BC | 15 | NR | NR | NR | NR | NR | NR |
|                          |                  |          |         | PC/BC | 28 | NR | NR | NR | NR | NR | NR |

BC, blended cut; EC, endocut; ES, endoscopic sphincterotomy; NR, not reported; PC, pure cut; PC/BC, pure cut followed by blended cut; SOD, sphincter of Oddi dysfunction.
Table 2. Network estimated risk ratios (RRs) of electrocautery modes on the risk of acute pancreatitis and risk of bleeding.

| Intervention | Acute pancreatitis | | | Bleeding | | |
| | Direct estimate, RR [95% CI] | Network estimate, RR [95% CI] | | Direct estimate, RR [95% CI] | Network estimate, RR [95% CI] | |
| Blended | | | | | | |
| Compared with | Endocut | 0.72 [0.18–2.9] | 0.81 [0.24–2.46] | 2.54 [0.51–12.72] | 2.25 [0.99–7.08] |
| | Pure cut | 1.99 [0.65–6.06] | 2.10 [0.92–5.69] | 0.47 [0.34–0.64] | 0.52 [0.26–1.41] |
| | PC/BC | 1.04 [0.43–2.50] | 1.19 [0.36–4.03] | 1.12 [0.20–6.11] | 0.83 [0.25–2.92] |
| Endocut | | | | | | |
| Compared with | Blended | 1.39 [0.34–5.59] | 1.24 [0.41–4.21] | 0.39 [0.08–1.97] | 0.44 [0.14–1.01] |
| | Pure cut | 3.59 [0.76–16.98] | 2.62 [0.76–11.56] | 0.35 [0.16–0.75] | 0.23 [0.08–0.65] |
| | PC/BC | – | 1.47 [0.31–7.83] | – | 0.37 [0.08–1.38] |
| Pure cut | | | | | | |
| Compared with | Blended | 0.5 [0.16–1.54] | 0.48 [0.18–1.09] | 2.13 [1.57–2.91] | 1.92 [0.71–2.91] |
| | Endocut | 0.28 [0.06–1.32] | 0.38 [0.09–1.32] | **2.86 [1.33–6.14]** | **4.30 [1.53–12.87]** |
| | PC/BC | 0.58 [0.31–1.09] | 0.57 [0.17–1.55] | 1.59 [0.73–3.49] | 1.58 [0.48–4.35] |
| PC/BC | | | | | | |
| Compared with | Blended | 1.04 [0.43–2.50] | 0.84 [0.25–2.82] | 0.90 [0.16–4.90] | 1.02 [0.34–3.95] |
| | Endocut | – | 0.68 [0.13–3.18] | – | 2.72 [0.72–12.95] |
| | Pure cut | 1.73 [0.92–3.26] | 1.76 [0.64–5.73] | 0.63 [0.29–1.38] | 0.63 [0.23–2.07] |

CI, confidence interval; PC/BC, pure cut followed by blended cut; RR, relative risk. Risk ratios marked with bold indicate statistically significant differences between the groups.
electrical currents when performing sphincterotomy. Sphincterotomy during ERCP is a common procedure with significant risk of harm, the most feared being post-ES bleeding and PAP. The electrical current mode may be closely related with the occurrence of these adverse events as suggested for the first time by Sherman et al.\textsuperscript{27} in 1998. The papillary apparatus is a richly vascularized tissue with arterial branches of the retroduodenal artery, a gastroduodenal artery tributary. As such, there is a risk for severe hemorrhage when one of those is accidentally sectioned. HF current can diffuse inside the adjacent pancreatic tissue, hence the risk of pancreatic injury and systemic inflammatory response. A trade-off is essential because more coagulation may be advantageous to avoid bleeding and less may be better to avoid PAP. Several studies have been conducted to better understand the link between electrocautery and acute pancreatitis\textsuperscript{7,19–24} as well as the patient’s and procedural characteristics associated with increased risk for post-ES adverse events. Risk factors for pancreatitis include suspected SOD, younger age, number of contrast injections into the pancreatic duct, precut sphincterotomy, and difficulty of cannulation.\textsuperscript{27–29} In close relationship with the latter, multiple cannulation attempts, perhaps related to excessive local trauma with subsequent tissue edema and transient pancreatic outflow obstruction, are also considered to increase the risk of PAP.\textsuperscript{30} Theoretically, a pure cutting current is likely to induce less edema of the ampulla after sphincterotomy, which should decrease the risk of pancreatitis if one accepts the potentially greater risk of post-sphincterotomy hemorrhage. The theory of post-sphincterotomy pancreatitis focuses on the hypothesis of incidental temporary obstruction of the pancreatic duct, as the passage of electrical current through tissue and subsequent thermal injury cause a significant increase in the permeability of capillary beds, which in turn allows leakage of macromolecules and fluid into the extracellular space, causing localized edema which reduces the duct lumen. However and in contrast to the above quoted and well-established risk factors, the relative role of different electrocautery modes in triggering PAP remains contradictory. In a first meta-analysis conducted by Verma et al.\textsuperscript{31} in 2007, the type of current used for sphincterotomy (PC versus BC) did not influence the incidence or severity of pancreatitis. However, PC current was associated with a higher incidence of bleeding in this study. Subsequently, both the American Society for Gastrointestinal Endoscopy and the European Society of Gastrointestinal Endoscopy recommended mixed current over PC in, respectively, their 2017 and 2019 biliary sphincterotomy guidelines.\textsuperscript{32,33}

In contrast, in an unpublished trial, Mitsushiro Kida et al.\textsuperscript{25} concluded that the EC current tended to decrease the incidence of bleeding and hyperamylasemia after sphincterotomy, without clear evidence in favor of a decreased rate of clinically overt PAP. However, this trial has not been published and has therefore not been included in this NMA. Several further meta-analyses attempted to determine the superiority, if any, of one electrocautery mode over another.\textsuperscript{31,34,35} Li et al. compared EC with blended current modes and found that the rate of post-ERCP pancreatitis was not significantly different during ES. However, contrary to our meta-analysis, the authors chose to mix RCT and non-RCT.\textsuperscript{36} Another more recent meta-analysis conducted by Funari et al.\textsuperscript{34} compared all different electrocautery modes in a pairwise fashion, but did not make use of the indirect evidence available. Similar to our results, Funari et al. found that PC carries a higher risk of mild bleeding compared with other electrocautery modes.

By pooling results from both direct and indirect evidence, we found confirmative evidence that PC was associated with a statistically higher risk of bleeding compared with other electrocautery modes. Also, we found that EC presented the lowest risk of bleeding (SUCRA rank probability: 98%). We can also state from our analysis that the available evidence does not support any advantage of one electrocautery mode over another vis-à-vis the risk of PAP. Although we found that PC has the highest chance of being the best electrocautery mode regarding the risk of pancreatitis (SUCRA rank probability: 63%), difference with other electrocautery modes was not statistically significant. Basing one’s assessment of efficacy on likelihood ranking can be misleading without an objective assessment of the strength of information in the network and the magnitude of absolute benefits that accompany rankings and can therefore be exaggerated, especially in the case of small differences in relative effects and limited information.\textsuperscript{11}

We recognize our study has several limitations. First, if all patients analyzed were enrolled in an RCT, which can minimize the risk of bias, a total of 1471 patients remains a relatively small sample.
size. Second, the total number of ERCPs performed in the different institutions analyzed is also an important factor influencing the medical complication rates and this could not be taken into account from the available data. Inclusion period of the first trial started in June 1994, before the advent of EC and with outdated current generators, and prevention measures with nonsteroidal anti-inflammatory drugs or hyperhydration had not yet been developed at the time of the earliest trials. Third, all studies were at high risk of bias in at least one domain of the Cochrane risk of bias tool. Pauclity and poor methodological quality of included studies may flaw overall results. Fourth, other preventive measures for acute pancreatitis such as the use of NSAIDs, intensive intravenous hydration, or prophylactic pancreatic stent were not reported. Fifth, bleeding definition was reported on a small number of study and definition was heterogeneous. Authors did not distinguish between intraprocedural and delayed bleedings. Immediate bleeding might be just minor, nonsignificant adverse event, which can be self-limiting or managed easily, consequently clinically less significant compared with delayed bleedings, which can require hospital readmission, reintervention, and transfusion.

The main finding of our meta-analysis is that EC current is better at preventing bleeding than PC. Mild bleeding can be easily controlled in most patients, but not in high-risk patients that mandate resuming anticoagulant or antiplatelet agents post-ES. In light of our results, we recommend the use of EC because of its protective effect with regard to bleeding and because no other mode has demonstrated superiority in decreasing the risk of PAP. It is worth noting that the more recent HF generators offer the ability to fine tune the amount of coagulation current in EC modes (i.e. the so-called ‘effect’ in certain models), which can be a way to optimize the balance between hemostasis and current diffusion in pancreatic tissue and tailor this to the type of papilla and individual patient risk. Such possible improvements in generator settings deserve further study.

Author contributions
Abdellah Hedjoudje: Conceptualization; Data curation; Formal analysis; Methodology; Writing-original draft; Writing-review & editing.
Chérifa Cheurfa: Conceptualization; Data curation; Formal analysis; Methodology.
Jad Farha: Conceptualization; Data curation; Formal analysis; Methodology.
Bénédicte Jaïs: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-review & editing.
Alain Aubert: Conceptualization; Data curation; Formal analysis; Methodology; Writing-review & editing.
Diane Lorenzo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology.
Frédérique Maire: Conceptualization; Data curation; Formal analysis; Methodology.
Dilhana Badurdeen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology.
Vivek Kumbhari: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Writing-original draft; Writing-review & editing.
Frédéric Prat: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing-review & editing.

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Writing assistance
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ORCID id
Abdellah Hedjoudje https://orcid.org/0000-0002-6389-828X

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